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Differential Effects of Modafinil on Performance of Fatigue Susceptible and Fatigue Resistant Individuals

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STATEMENTS

Disclaimer

The views expressed in this technical report are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government.

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Human Research/Institutional Review Board (IRB) statement

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

Background*:* Individual responses to the effects of inadequate sleep have been well documented, indicating that some people are more vulnerable to the effects of sleep loss than others. The extant literature generally divides these individual responses into two groups: fatigue-vulnerable and fatigue-resistant individuals. Fatigue-vulnerable individuals generally require access to effective fatigue countermeasures in order to maintain their alertness and performance. However, a question arises as to whether or not these fatigue-vulnerable individuals, once administered an alertness aid, can receive the same benefits shown in group efficacy data. The present study administered modafinil to fatigue-vulnerable and -resistant individuals to determine its differential effects on performance.

Methods*:* Performance from 22 individuals was measured on 2 separate occasions during approximately 36 hours of continuous wakefulness each test period. During one period, they received 200mg modafinil and during the other period they received placebo, determined by random assignment. Participants were tested on a variety of cognitive, physiological, and subjective measures at 5-hr intervals across the continuous wakefulness period. Performance from the placebo testing period for each metric was used to group individuals into either fatigue-vulnerable or fatigue-resistant groups.

Results*:* Performance on each task was analyzed to determine whether modafinil benefited the fatigue-vulnerable and fatigue-resistant groups differently. Results indicated that, after receiving modafinil compared to placebo, those in the fatigue-vulnerable group improved significantly on the number of correct responses and reaction time on the Stroop task, whereas the fatigue-resistant group's performance did not change. In the DMTS task, the fatigue-resistant group showed stable performance throughout the testing period, regardless of whether they received modafinil or not; however, the fatigue-vulnerable group significantly improved after receiving modafinil compared to their performance after receiving placebo. There were fewer lapses on the PVT in the fatigue-vulnerable group after modafinil than after placebo; modafinil also benefited performance in the fatigue-resistant group, but not to the same extent as in the vulnerable group. However, performance was not affected differently by administration of modafinil for either group on the RDM task or the WCST. Measures of brain activity (EEG and ERP) were not altered by modafinil in either group except for alpha activity; fatigue-resistant individuals showed less alpha activity after modafinil than after placebo whereas the fatigue-vulnerable individuals did not show a benefit. Subjective measures of fatigue did not change within each group, regardless of drug condition.

Conclusions*:* Generally, fatigue-resistant individuals did not benefit substantially when administered modafinil compared to no intervention. However, the fatigue-vulnerable individuals showed improvement in performance after receiving modafinil compared to no intervention. These effects appear to be task-dependent. Tasks that evaluated the cognitive abilities of working memory and vigilance demonstrated the greatest performance increases post-modafinil in fatigue-vulnerable individuals.

1.0 INTRODUCTION

Sufficient sleep has been recognized as a key factor in the success of a mission or field operation (Lindsay & Dyche, 2012), and is comparable to maintaining adequate food and transportation logistics (Angus, Pigeau & Heslegrave, 1992). However, the amount of sleep the average adult obtains each night has decreased over time. In 1985, the average sleep duration was 7.4 hours, with 22.3% of adults reporting sleeping less than 6 hours per night; in 2012, the average sleep duration was 7.18 hours, with 29.2% of adults reporting sleeping less than 6 hours per night (Ford, Cunningham, & Croft, 2015). The detrimental effects of sleep loss, both in the civilian workplace (Dawson & McCulloch, 2005; Krueger, 1989; Lerman, Flower, Gerson, & Hursh, 2012) and in military operations (Giam, 1997; Lindsay & Dyche, 2012; Miller, Matsangas, & Shattuck, 2007) have been well documented. For example, fatigue due to sleep loss has been named as a contributing factor in 12% of the Air Force's Class A mishaps and 4% of the Army's Class A-C mishaps (Caldwell & Caldwell, 2005). Revealing the extent to which sleep loss is plaguing military personnel, Troxel and colleagues reported over 62% of military members surveyed slept 6 hours or less per night and many reported poor sleep quality (Troxel et al., 2015). Furthermore, long duty periods, high workload situations, circadian disruptions, and insufficient recovery time between flights or missions ensures that fatigue will continue to be a problem for military personnel (Caldwell et al., 2009; Neville, Bisson, French, Boll, & Storm, 1994; Samel, Wegmann, &Vejvoda, 1995).

The neurobehavioral effects of total sleep deprivation are clear and pronounced; impairment of various functions occurs quickly and increases in a relatively linear fashion with a slight diurnal recovery due to natural fluctuations in the circadian rhythm. During the circadian trough, the low-point in the body's circadian rhythm that generally occurs between 0200 and 0600, alertness is lower, reaction time is slower, and accuracy is poorer than during the circadian peak (i.e., during daytime hours) (Folkard & Tucker 2003). Numerous reviews provide a comprehensive assessment of the effects of inadequate sleep, including an increase in involuntary microsleeps, attentional instability, and judgment errors with a simultaneous decrease in response speed, response accuracy, learning, task-shifting ability, and situational awareness (Balkin, Rupp, Picchioni, & Wesensten, 2008; Banks & Dinges, 2011; Lim & Dinges, 2010; Killgore, 2010).

When adequate sleep is either impossible or impractical, like in many military operations, there are a number of countermeasures that can be implemented to mitigate fatigue-related cognitive impairments (Caldwell et al., 2009; Caldwell, Caldwell, Thompson, & Lieberman, 2019). For example, napping has been shown to enhance alertness and performance in sleep-deprived individuals in both operational situations (Naitoh & Angus, 1987) as well as civil aviation (Deuster, Weinstein, Sobel, & Young, 2009; Rosekind et al., 1995). However, when sleep, even a short nap, is not obtainable due to operational tempo, alertness aids are available for use in some U.S. military operations. The U.S. Army, Air Force, and Navy allow either dextroamphetamine or modafinil during certain operations to enhance alertness and safety. These prescription alertness aids are effective in both laboratory and operational settings; however, information regarding individual responses to sleep deprivation and subsequent countermeasures are unclear and may be useful to physicians and commanders when deciding when and to whom alertness aids should be prescribed.

The role of physiological differences among individuals with regard to effectiveness is becoming increasingly important in work environments, especially considering the increasingly important role of the individual in determining mission success. For example, during World War II, a thousand B-17 aircraft were required to destroy one target, requiring 10,000 crewmembers to accomplish the mission. In our current system, a mission with 16 targets can be carried out by *one* highly sophisticated, $2 billion B-2 aircraft with a 2-member crew (Robb & Ortega, 2012). This example typifies the current state of military operations; jobs are increasingly being performed by fewer people operating highly automated, expensive equipment. But the progress in technology may be exceeding the capabilities of human physiology. The pace and temporal organization of operations often forces warfighters to perform in sleep-deprived conditions. This compounded problem poses serious risk in safety-sensitive jobs; knowing the full capabilities of an individual has become paramount to mission success.

Sleep deprivation affects individuals differently. Performance decrements are evident among some personnel after only a short period of sleep deprivation, whereas others can maintain performance after relatively longer periods of sleep loss (Van Dongen, Bender, & Dinges, 2012). Results from numerous studies show that individual differences are robust, stable traits which consistently characterize individuals' responses to inadequate sleep (Leproult al., 2003; Rupp, Wesensten, Bliese, & Balkin, 2009; Van Dongen, Baynard, Maislin, & Dinges, 2004; Van Dongen, Maislin, Mullington, & Dinges, 2003). The importance of these individual responses was noted by Van Dongen (2006) who reported that the majority of workplace accidents occurring during the night shift were caused by a small number of workers. Identification of fatigue-vulnerable individuals will allow tailored implementation of fatigue countermeasures, providing aids, such as modafinil, to those who need it most while avoiding unnecessary dosing of those who do not. Through tailoring pharmaceutical countermeasures by fatigue susceptibility, mission effectiveness and safety will increase while the resilience of fatigue-vulnerable individuals will improve. While the military mission, and therefore use of countermeasures, differs from that of the general public, many tasks require similar skills, and thus information gained from implementation of specific countermeasures offers options to civilian workforces who may benefit from comparable strategies. For example, emergency workers (e.g., firefighters, emergency medical teams, etc.) may justify use of modafinil if individualized dosing schedules are delineated.

Once an individual's response to fatigue is identified, appropriate action can be determined. One potential application of current fatigue countermeasures may be selective use based upon fatigue susceptibility. For example, anecdotal reports from the operational communities indicate that some individuals consume an alertness aid (go-pill) on a long mission, whereas others return with their full allotment (Gore, Webb, & Hermes, 2010). Could go-pills be distributed on an individual need based on fatigue vulnerability? Can we improve performance in fatigue-vulnerable individuals during periods of sustained wakefulness to a similar level as the fatigue-resistant individuals?

The present study addressed this latter question of whether modafinil can increase performance levels of individuals susceptible to the effects of sleep deprivation to comparable levels of those who are resistant. Following training and baseline measures on various cognitive assessments, participants were tested over 2 separate periods of 36 hours of continuous wakefulness.

Participants received 200mg of modafinil during one period of wakefulness and placebo during the other wakefulness period. Performance was assessed to determine which participants from this sample were fatigue resistant (performance does not notably decline) and which participants were fatigue vulnerable (performance markedly declines), forming two groups based on fatigue susceptibility. Performance was compared between two groups to determine if modafinil elevated performance of the fatigue-susceptible group to at least the same level as those who were fatigue resistant, as well as to determine if the fatigue-resistant group benefited significantly from modafinil.

Hypotheses tested:

1) Fatigue-vulnerable individuals who are administered 200mg of modafinil will perform on a variety of tests as well as fatigue-resistant individuals who are given modafinil during a period of continuous wakefulness.
2) After consumption of 200mg of modafinil, improvement in the cognitive performance of fatigue-vulnerable individuals will be greater than improvement in fatigue-resistant individuals.

2.0 METHOD AND PROCEDURES

The protocol was a mixed-model, double-blind placebo-controlled study in which participants were tested in two separate periods during which they were kept awake for approximately 36 hours each testing period. During one test period, they received 200mg modafinil; during the other test period, they received a placebo. The conditions were counterbalanced so that one half of the participants received the active drug during the first test period and the other half received the active drug during the second test period. The protocol was approved by the Naval Medical Research Unit Dayton Institutional Review Board (NAMRU-D 2016.0016).

2.1 Pre-study questionnaires and assessments

2.1.1 Questionnaires. The following is a list of assessments taken on the 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) which may impact one's response to sleep deprivation (Killgore, Richards, Killgore, Kamimori, & Balkin, 2007; Taillard, Philip, Coste, Sagaspe, & Bioulac, 2003).

2.1.1.1 The Horne and Östberg Morningness/Eveningness Questionnaire (MEQ) (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 with companion software.

2.1.1.2 The Revised NEO Personality Inventory (NEO-PI-R™) was used for the assessment of personality (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. Participants answered this questionnaire on a printed copy. A research staff member scored the completed questionnaire from the template provided by Psychological Assessment Resources, Inc.®.

2.1.2 Activity/sleep monitor. Sleep/wake data were collected to ensure participants attained adequate sleep each of the 3 days prior to their training day. The *Motionlogger Micro Sleep Watch*® (wrist activity monitor) from Ambulatory Monitoring, 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 was used to collect movement data. The movement results were plotted using accompanying software to track participants' sleep patterns. Participants were instructed to wear the wrist activity monitor 3 days prior to both in-house portions of the study. The data were downloaded and reviewed for compliance with the sleep requirement on 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 dismissed from the study.

2.2 Performance tests and questionnaires

The following is a list of cognitive tasks, questionnaires, and physiological assessments included in the study to evaluate individual responses to modafinil and effects of sleep deprivation on performance, mood, and physical state.

2.2.1 Cognitive and physiological measures. A series of cognitive evaluations were collected during the training, baseline, and continuous wakefulness periods. Tests measured a variety of cognitive functioning, including participants' ability to maintain attention, reaction time, memory, and psychomotor tracking. Tests from the NTI Armory Test System (ATS)™ battery of tests (NTI, Inc., Fairborn, OH) are noted where appropriate.

2.2.1.1 Psychomotor Vigilance Test (PVT). Vigilance 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 was asked to press a microswitch as quickly as possible once the numbers were displayed and the device recorded reaction time and any trial lapses (reaction times greater than 500ms). The interstimulus interval varied 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. Figure 1 shows the PVT device.

Figure 1. The Psychomotor Vigilance Test (PVT)

2.2.1.2 The Stroop Task (NTI ATS™) demonstrates the concept of interference in a reaction time task. The name of a color (e.g., blue) is printed in a font color that may or may not be descriptive of the name (e.g., the word "blue" is printed in green font; see figure 2 for an example of when the font color is descriptive and not descriptive of the word). The time required to name the color of the text requires more effort when text and font color do not match (e.g., the word blue written in green font, an incongruent stimulus) than if the word is printed in the same font color (e.g., "blue" is printed in blue font, a congruent stimulus). In this version of the test, stimuli were presented one at a time on a computer screen, easily read even by someone with mild visual acuity deficit. The stimuli, consisting of highly saturated colors of red, blue, and green appeared in the center of the screen until the person responded or the trial timed out (5 seconds) until a total of 100 stimuli were presented. The participant was to respond using a mouse as quickly and accurately as possible. The test word was either a congruent word, an interference word (incongruent color word), or a neutral word. The neutral words were "gun," "door," and "house." The display color and the neutral words were paired randomly. Within each set of stimuli, the required response was to name the color and ignore the word. Each possible pair appeared randomly with the constraint that they appeared approximately equally often over the course of the test. There were 18 possible combinations for all 3 colors. The data from this test included the number of correct and incorrect responses, percent correct, and the mean and standard deviation of correct and incorrect responses for congruent, incongruent, and neutral stimuli.

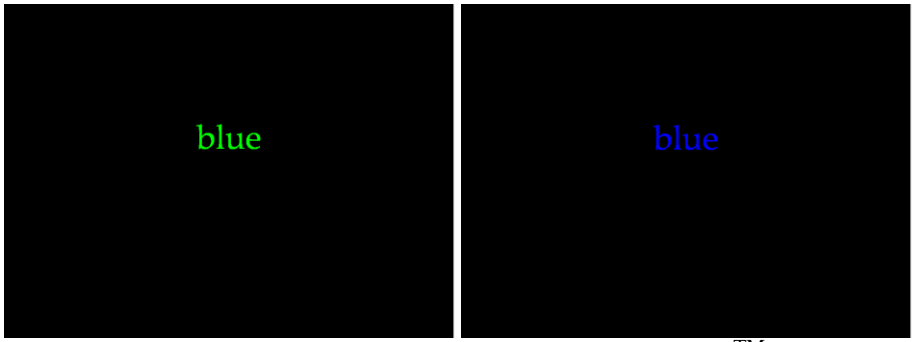


Figure 2. The Stroop Test from the NTI ATS™

2.2.1.3 Rapid Decision Making Task (RDM) (NTI ATS™). This test measures the ability to quickly examine and act upon visual stimuli in the context of the task's stated rules. Participants

were shown several levels represented by overlapping ring sections with each level equating to a different threat level (red = critical, yellow = danger, green = alert). At various intervals, different “vehicles” were indicated somewhere on the display. Each vehicle's symbol was ranked according to its possible danger (“?” = minimal danger, “O” = medium danger, and “X” = high danger). Participants were instructed to assess the threat posed by a given vehicle based on its location as well as the danger associated with each vehicle’s symbol and indicate which vehicle was the greatest threat. Participants were instructed to weigh the vehicle’s location more heavily than the threat level classification. For example, a medium threat symbol “O” placed in the critical area (red) should be perceived as a greater threat than the symbol “X” placed in the alert area (green). Examples are shown in Figure 3 below. In panels 1 and 2, "X" poses the greatest threat; in panel 3, "O" poses the greatest threat. The data from this test included number correct and correct reaction time.

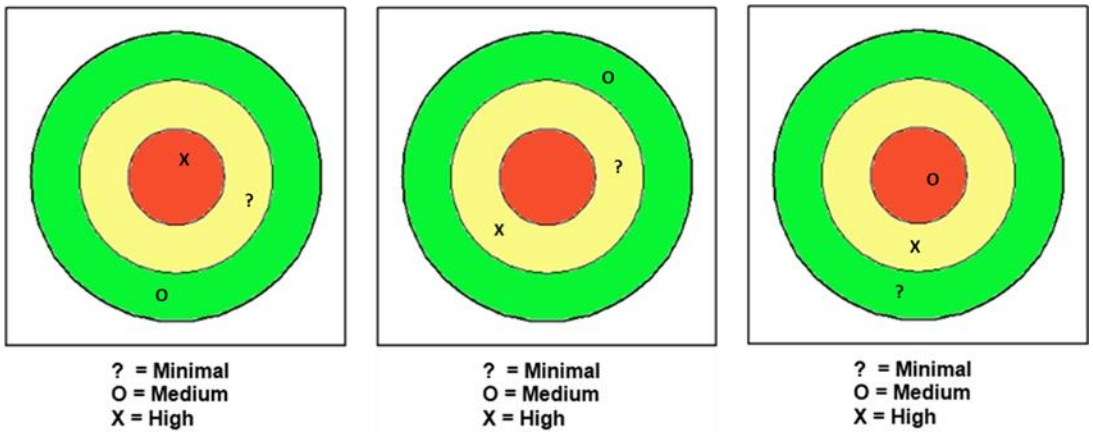


Figure 3. The Rapid Decision Making Task from NTI ATS™

2.2.1.4 Delayed Match to Sample Task (DMST) (NTI ATS™). This task is designed to assess working memory and pattern recognition skills by quickly and accurately choosing a test stimulus which is identical to a standard stimulus presented previously. This task consisted of three separately presented parts: initial matrix presentation, interference, and test trial. Participants were initially presented with a 4 x 4 checkerboard matrix design. After viewing the sample matrix stimulus for a time adequate for committing the stimulus to memory (maximum view time was 60 seconds), the participant pressed the left mouse button to clear the screen and initiate the interference stimulus. The interference stimuli consisted of 4 alphabet characters presented for 4 seconds when a vowel was present and 25 seconds when a vowel was not present and required the participants to determine if the letter string contained a vowel. The participant pressed the left mouse button if a vowel was present, and the right mouse button if no vowel was present. Afterward, the test trial was presented which consisted of two matrices side by side on the screen. One of the matrices was identical with the initial sample matrix while the other was different. The participant responded with the mouse button (right or left) corresponding to the test matrix that was identical to the initial sample matrix with a maximum viewing time of 30 seconds. The sequence of stimuli is shown in Figure 4. The data from this test included number correct and correct reaction time.

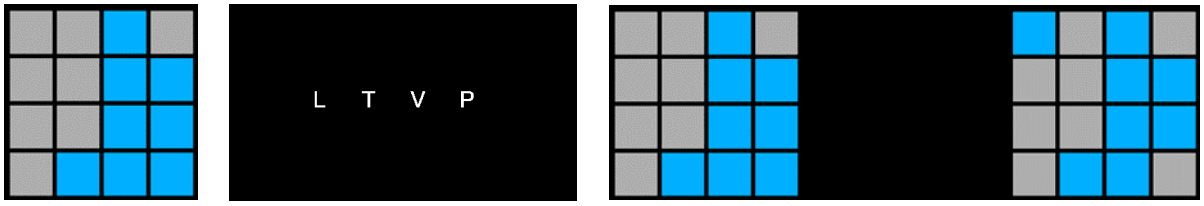


Figure 4. Delayed Match to Sample task from NTI ATS™
First image: Initial matrix; Second image: Interference stimulus; Third image: Test trial

2.2.1.5 The *Wisconsin Card Sorting Task (WCST) (NTI ATS™)* assesses set-shifting, or cognitive flexibility in response to changing environmental contingencies. Relying heavily on working memory, the test is considered a good measure of frontal lobe functioning and demonstrates the ability to learn concepts.

Four groups of figures (called "key cards") were shown to the participant on the computer monitor. Each "card" showed varied shapes (triangle, star, plus, and circle), color (red, green, yellow, and blue), and number of shapes (one to four).

Figure 5. Wisconsin Card Sorting Task from NTI ATS™

The participant was then presented with a series of "test cards" containing various combinations of the shapes, colors, and number of objects shown in the key cards. The task was to decide which key card "matches" the presented test card. Since there are three different ways a test card can match a key card (by color, shape, or number), the participant must learn which sorting criterion to use. No rule was given to the participant for matching cards. However, feedback was given for each attempted match on whether it was "correct" or "incorrect." This was based on a pre-established sorting criterion.

Once the participant discovered the correct sorting criterion (color, shape, or number) and correctly matched six consecutive times, the criterion switched to one of the other two criteria. If the participant made an error before executing six consecutive correct trails, the count started over (i.e., the participant answered correctly five consecutive times, but then answered incorrectly). There were nine series of criteria shifts designed to present each sorting criterion an equal number of times. If the test went on for more than nine series before the participant "passed," a new series was begun. The test continued until the participant successfully switched criterion four consecutive times, or until 72 test cards were presented, whichever came first.

The four key cards were presented at the top of the screen, evenly spaced, with enough distance between cards that errors could not be attributed to poor visual-motor control. Test cards appeared centered near the middle of the screen beneath the key cards. These appeared one at a time, simulating the card "deck." The participant used buttons on the keyboard to select the key

card he thought was the match for the test card. There was immediate feedback on the correctness of the response, based on the active criterion, which appeared at the top of the screen.

Data collected included time to complete the test (in seconds), number and percent of correct responses, number and percent of incorrect responses, total number of perseverative responses (times past criterion were used post-criterion change), number of attentional lapses, number of criterion shifts, and number of failures to maintain set (shifting criterion before six correct responses).

2.2.1.6 Oculometric assessments. 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 the present state on four pupillometric variables (saccadic velocity, pupil diameter, pupil constriction amplitude, and pupil constriction latency) to baseline state data. This task was completed during each session. Each trial required approximately 30 seconds to complete. Figure 6 illustrates the posture of the participant when viewing the stimuli from the FIT.

Figure 6. The PMI FIT device

2.2.1.7 Contrast visual acuity was assessed using the Tumbling "E" optotypes (Taylor, 1977) at a distance of 4 m (see figure below). Each row on the chart consisted of equally-spaced E's that decreased in size at each subsequent lower row. Each row represented a specific visual acuity when viewed at 4 m. Snellen equivalent acuity ranges from 20/200 (top of chart) to 20/10 (bottom of chart). Four different chart orientations were utilized to reduce participant memorization. Overhead room lights were turned off and the chart was viewed using a backlit light source (Precision Vision chart illuminator, model 2425) that produced approximately 5 lux of received illuminance at the 4 m viewing distance. After 5 minutes of dark adaptation, each participant was instructed to view the chart, find the smallest row he/she could see, and state which direction each "E" on the line was facing. If all of the "E" orientations in the row were identified correctly, the experimenter asked the participant to view the next smallest row until the participant no longer responded with 100% accuracy for the entire row. The smallest acuity size targets identified with 100% accuracy served as the participant's score. Acuity contrast of 1.25%, 2.5%, 5%, 10%, 25%, and 100% were measured for the participant's right eye only. Charts were rotated 90 degrees prior to each session. Maximum acuity for each contrast level for the right eye was represented in LogMAR, Snellen, and decimal equivalents. See figure 7 for an example of a tumbling E chart.

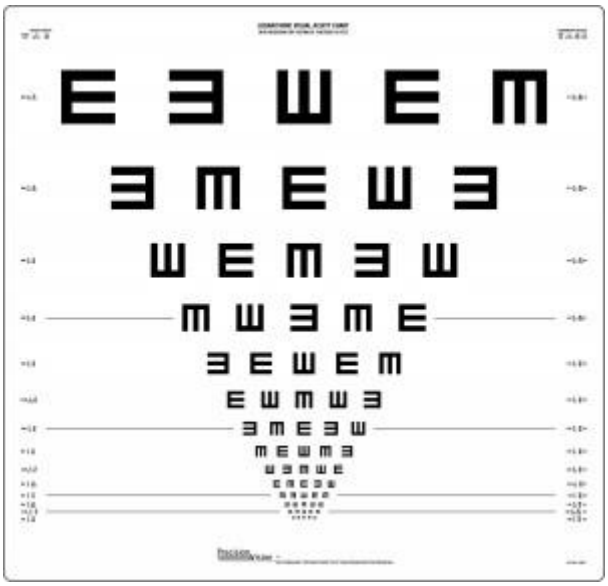


Figure 7. The Tumbling E Chart

The contrast acuity data were sent to collaborators at the U.S. Army Aeromedical Research Laboratory (USAARL). The investigators at USAARL will analyze the data from this test and present the results in a separate report.

2.2.1.8 Resting electroencephalogram (EEG) recordings during eyes closed and eyes open were collected during each session of the study. These data were collected and stored with the Grass Technologies AS40-PLUS amplifier system and TWin® acquisition and review software. Electrode sites for the EEG were the standard sites per the Jasper 10-20 system (Jasper, 1958), with additional channels for Oz, FPz, ground, left and right mastoids, and reference. Preparation for collection of the EEG data included refilling each electrode with electrolyte gel (up to 20 EEG channels, referenced to the averaged mastoids during recording). In order to record eye movements and blinks, electro-oculogram (EOG) data were collected from electrodes affixed to the outer canthus of each eye (bipolar) and from the upper and lower centers of each eye (bipolar). The time constant used for the EEG channels was 0.3 seconds, and the high cutoff filter was 35 Hz and the low cutoff filter was 0.1 Hz; the sampling rate was 400 Hz. For EOG, the time constant was 5.0 seconds, and the high filter was 10 Hz. The 60 Hz notch filter was used as necessary. Participants were seated in a chair and asked to sit quietly while data were recorded. The participant's eyes-open EEG was recorded for approximately 2 minutes, followed by approximately 2 minutes of eyes closed, but awake, EEG.

2.2.1.9 Auditory event-related potentials (ERP) were recorded using a variation of the P300 oddball task described by Duncan-Johnson and Donchin (1977). The one-second ERP epochs were derived from electrodes placed along the participant's scalp in accordance with the 10-20 system of electrode placement (Jasper, 1958). Binaural tone signals of either 1000 Hz (high-probability signals) or 1500 Hz (low-probability signals) were presented through Shure SE 315 in-ear sound isolating earphones for a duration of 60 msec per signal at a sound pressure level of 61 dB. Signals were presented using a variable inter-stimulus interval within a continuous 66 dB

white-noise background. Three-hundred and sixty high-probability and 40 low-probability (oddball) tones were presented in each experimental trial, lasting a total of approximately 24 minutes. Each tone signal was inserted at random within a temporal envelope of 3500 msec with the caveats that there must be at least 1000 msec between the termination of a tone and the onset of the ensuing tone, that there must be one low-probability signal placed within a block of every 10 signals, and that two low-probability tones could not occur in sequence. Low- (35 Hz) and high- (0.3 Hz) pass filtered EEG were sampled at 400 Hz (i.e., one sample every 2.5 msec). Eye movements and blinks were recorded from the same six EOG electrodes used for the resting EEG montage. All scalp and eye-movement channels utilized an average mastoid reference. Participants were seated in a chair and instructed to first center their gaze on a bullseye target located approximately 30 inches in front of their line of sight (to minimize saccades). During the test, participants indicated their detection of each low-probability tone by pressing a handheld button switch as quickly as possible. Both speed and accuracy of responses were recorded. Metrics recorded during task participation included P300 latency and amplitude as well as reaction time and accuracy of target stimulus identification.

2.2.1.10 Vital signs (heart rate, temperature, and blood pressure; Welch-Allyn Spot Vital Signs, Welch-Allyn, Inc.) were measured for each participant during each test session in order to determine any differences which may occur between baseline and treatment conditions.

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

2.2.2.1 The POMS (McNair, Lorr, & Droppleman, 1981) is a 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 items in the questionnaire. The questionnaire was administered and scored by computer.

2.2.2.2 The VAS is a self-report measure of adjectives reflecting mood states of ‘alert/able to concentrate’, ‘anxious’, ‘energetic’, ‘feel confident’, ‘irritable’, ‘jittery/nervous’, ‘sleepy’, and ‘talkative’ (Penetar et al., 1993). Each adjective is presented with a 100mm line centered above each word. At the extremes of each line, ‘not at all’ and ‘extremely’ were printed, respectively, with ‘not at all’ located at the far left of the line. Using the computer mouse, participants indicated where on the line they felt their mood was best represented. Scores consisted of the distance of the mark from the left end of the line (in mm), with higher scores indicating an increased presence of the stated mood. The questionnaire was presented on a computer screen and scored by computer program.

2.2.2.3 Side effects were assessed via a questionnaire. Participants were shown a list of possible symptoms which included those associated with stimulant use and/or sleep deprivation (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.” This questionnaire was presented and scored by computer.

2.2.3 Biological samples. Breath and saliva samples were collected in an effort to identify potential biomarkers for fatigue.

2.2.3.1 Blood samples. For each data collection period, blood samples were collected via venous phlebotomy by a certified medical laboratory technician using standard antiseptic procedures into PAXGene™ Blood RNA tubes (Qiagen/PreAnalytiX). An indwelling venous (IV) catheter was placed in the arm or hand through which blood samples were drawn. Venous phlebotomy was performed every 4 hours beginning at 1210 on Day 1 with the last sample at 1610 on Day 2 (see testing schedule in Table 1 below) for a total of 8 collections. All participants were in a sitting or supine position during needle insertion. Blood collection was in accordance with the 4TOX1QTP (Qualification Training Package Module 11: "Collect Blood Specimens"). The IV line was cleared by collecting approximately 1 mL in a red-top serum tube (BD Vacutainer®), approximately 4mL were collected in an oxalate/fluoride tube (BD Vacutainer®), and then approximately 2.5 mL of blood were collected into the PAXgene™ tube. The line was then flushed with normal saline. To maintain IV clear lines before draws, a heparin flush (up to 2.5 mL, 10U/mL) was used. The total blood draw volume for each study session (8 collections) was no more than 86 mL (about 6 Tbsp), well within the limits allowed under Office of Human Research Protection (OHRP) guidelines for healthy participants. In each instance, the IV line was flushed with saline and heparin to ensure the IV line remained clear between blood draws. If the IV line became clogged and the blood sample could not be drawn through the IV catheter, with the participant's consent, and at the phlebotomist's and/or medical consultant's discretion, the clogged IV catheter was removed and another IV catheter was inserted and/or blood was drawn with a venous puncture, as appropriate, to obtain blood samples.

Blood samples were sent to the Federal Aviation Association (FAA) for gene expression analysis of coding and noncoding RNAs and to determine modafinil concentration in each sample. These data will be analyzed and the results presented in a separate report.

2.2.3.2 Breath samples were collected from a subset of the volunteers. Exhaled breath were collected using a 5L polypropylene bag affixed with Teflon™ breathing tubes. Participants were instructed to first normally exhale some air into the room and then inflate the bag using the remaining alveolar air from the lungs, termed "post-tidal breath." This process was repeated until the 1L bag was approximately 50% filled. The breath samples were collected 6 times at 7, 11, 19, 23, 31, and 35 hours after awakening for a total of 6 samples. These data were collected for researchers affiliated with Universal Technology Company (UTC) under a Cooperative Research and Development Agreement (CRADA). UTC will analyze these data and submit a separate report.

2.3 Participants

Participants were military men between the ages of 21 and 40. Exclusion criteria included daily consumption of more than 250mg of caffeine; a history of significant psychiatric, neurological, or sleep-related problems; tobacco use within the last 6 months; insufficient sleep for the 3 days prior to the study days; and any medication use. Participants were compensated for their time and effort.

2.4 Description of study

All participants were tested in the Naval Medical Research Unit Dayton (NAMRU-D) Fatigue Assessment and Countermeasures (FAC) lab. Participation in this study consisted of two testing visits to the laboratory; each visit occurred over two days. Participants arrived at the FAC lab for training on the cognitive tests at 0800 on Day 1 and completed all intake procedures. The actigraph was checked to make sure participants met the sleep requirements (at least 7.5 hours in bed with at least 7 hours of sleep for 3 nights immediately preceding the in-house portion of the study and a rise time of 0600 the morning of the training day). If the sleep requirements were not met, the participant was given the option to reschedule or was not enrolled in the in-house portion of the study. Once the sleep requirement was confirmed, participants completed the Horne and Östberg Morningness/Eveningness Questionnaire and the NEO-Pi-R™ and began electrode hook-up.

On Day 1 of each visit, participants completed two training sessions to obtain performance asymptote to avoid learning effects once testing began. The last session on Day 1 was the baseline session after which the participant remained awake and began the sleep loss period of the study (Day 2), experiencing a total of 36 hours of continuous wakefulness. Participants received either 200mg modafinil or a placebo at 2400 hrs (18 hours awake) prior to an additional 18 hours of continuous wakefulness. At the end of the last PVT on Day 2, participants were debriefed and dismissed. They were not allowed to drive themselves home. The following week, participants returned to the laboratory to complete the second testing visit. This second visit was exactly like the first, with two training sessions followed by a baseline session (Day 1) and sleep deprivation sessions (Day 2). Participants were debriefed and dismissed following the last PVT of Day 2. Again, they were not allowed to drive themselves home. The testing schedule is outlined in Table 1. The intra-session schedule is outlined in Table 2. Table 3 outlines the time for the PVTs, administered every hour starting at 1200, along with the blood and breath sample times.

Table 1. Daily testing schedule

Time	Day 1 Training/Baseline	Day 2 Deprivation
0000		DRUG DOSE
0100		
0200		Session 1
0300		
0400		
0500		
0600	Wake-up	Session 2
0700		
0800	Arrive at NAMRU-D	
0900	Electrode hook-ups; questionnaires	Session 3
1000		
1100		
1200		
1300		
1400	Training 1	Session 4
1500		
1600		
1700		Debrief/Dismiss
1800	Training 2	
1900		
2000		
2100		
2200	Baseline	
2300		

Table 2. Testing session schedule

Minutes from start of session	Task
00	PVT
15	Vision (acuity)
30	Vision (PMI)
35	NTI Battery:
	Stroop
	RDM Task
	WCST Task
	DMS Task
60	PVT
90	Resting EEG
95	ERP
120	PVT
130	POMS/VAS/SE
180	PVT

Table 3. Testing schedule for PVT, blood and breath samples

Time	Day 1 Training/Baseline	Day 2 Deprivation
0000		DRUG DOSE/PVT13/Blood sample
0100		Breath Sample/PVT14
0200		PVT15
0300		PVT16
0400		PVT17/Blood ample
0500		Breath sample/PVT18
0600	Wake-up	PVT19
0700		PVT20
0800	Arrive at NAMRU-D	PVT21/Blood sample
0900		PVT22
1000		PVT23
1100		PVT24
1200	PVT1 /Blood sample	PVT25/Blood sample
1300	Breath sample/PVT2	Breath sample/PVT26
1400	PVT3	PVT27
1500	PVT4	PVT28
1600	PVT5/Blood sample	PVT29/Blood sample
1700	Breath Sample/PVT6	Breath sample/PVT30/ /Debrief/Dismiss
1800	PVT7	
1900	PVT8	
2000	PVT9/Blood Sample	
2100	PVT10	
2200	PVT11	
2300	PVT12	

3.0 RESULTS AND DISCUSSION

The SPSS statistical software package Version 25 (International Business Machines Corporation®, Armonk, NY) was used to analyze the data from each task and questionnaire. Data were screened for outliers and were excluded from the analyses if a baseline score was 3 or more standard deviations from the overall mean. Analyses were conducted on each of the cognitive tasks to directly test the stated hypotheses.

Hypotheses tested:

1) Fatigue-vulnerable individuals who are administered 200mg of modafinil will perform on a variety of tests as well as fatigue-resistant individuals who are given modafinil during a period of continuous wakefulness.
2) After consumption of 200mg of modafinil, improvement in the cognitive performance of fatigue-vulnerable individuals will be greater than improvement in fatigue-resistant individuals.

A sample of 29 individuals enrolled in the protocol, with 22 successfully completing both data collection periods. The 7 participants who dropped out of the study discontinued for various reasons, mainly due to self-reported discomfort associated with sleep deprivation. All

participants were male active duty military between the ages of 21 and 40 (*M* = 28.50, *SD* = 5.59). The demographic characteristics are shown in Table 4.

Table 4. Demographics of sample (*M, SD*)

N	Age	Horne-Östberg MEQ Score	NEO-PI-R Neuroticism Score	NEO-PI-R Extraversion Score	Epworth Sleepiness Score
22	28.50 (5.59)	50.23 (10.09)	74.55 (18.89)	108.27 (19.66)	5.73 (2.99)

The amount of sleep obtained for the three nights prior to each participant's data collection period was averaged and analyzed to determine if the amount of sleep differed between the two testing periods. The *t*-test comparing the first data collection period with the second was not statistically significant ($t(21) = 1.372$, $p = .185$). The average amount of sleep obtained by participants before the first testing period was 8.33 hours (*SD* = 0.48) and 8.16 hours before the second testing period (*SD* = 0.52).

3.1 Initial analyses

Before analyzing the data based on fatigue response, all data were analyzed as one group of participants in the traditional manner to show the effects of modafinil and sleep deprivation on the performance of the sample as a whole. For each measure, a two-way, repeated-measures analysis of variance (ANOVA) was conducted with drug (modafinil and placebo) and session (the baseline session and sessions 1 through 4) as the repeated factors. Each analysis yielded three *F*-tests: a main effect of drug, a main effect of time (session effect), and a drug by time interaction. Mauchly's Test of Sphericity was used to test the assumption of sphericity. When the sphericity assumption was violated, the Huynh-Feldt correction and *F*-statistic are reported. The results of the Mauchly's Test of Sphericity are reported only when the assumptions were violated. Significant interactions were followed with analyses of simple effects and Fisher's Least Significant Difference (LSD) post hoc tests. Significant main effects for session were further analyzed with LSD tests. All results are presented by task below and are summarized in Appendix A.

3.1.1 Cognitive and physiological measures. Sleep-deprivation-related cognitive function was assessed using a series of cognitive tests administered during the baseline and testing sessions. Tests measured a variety of cognitive functioning, including participants' ability to maintain attention, reaction time, memory, and psychomotor tracking. Most of the cognitive tests were presented from the NTI ATS™ battery of tests and will be indicated as such. Unless noted, *N* = 22 for each condition.

3.1.1.1 Psychomotor Vigilance Test (PVT). Unlike the other tests which were administered once each test session, the PVT was administered every hour starting at 1200 on Day 1 with the last test at 1700 on Day 2, resulting in a 2 (drug) by 30 (session) repeated measures ANOVA. The metrics analyzed for this task were the number of lapses (RTs > 500msec) and the reciprocal reaction time (RRT). Due to a high number of lapses before sleep deprivation occurred (lapses

more than 3 standard deviations from the mean), 3 participants were excluded as outliers for this analysis, leaving a sample size of 19.

Lapses: Due to the number of sessions included in this analysis, Mauchly's Test of Sphericity was not computed, therefore, the assumption of sphericity was assumed. There was a significant interaction between drug and session ($F(29, 522) = 8.510$, $p < .001$, $\eta_p^2 = .321$). Post hoc analyses of the drug by session interaction indicated differences between the drugs starting at session 15 and continuing throughout the remainder of the sessions (except for session 26) with fewer lapses in the modafinil condition than the placebo condition. The effect is illustrated in Figure 8 below.

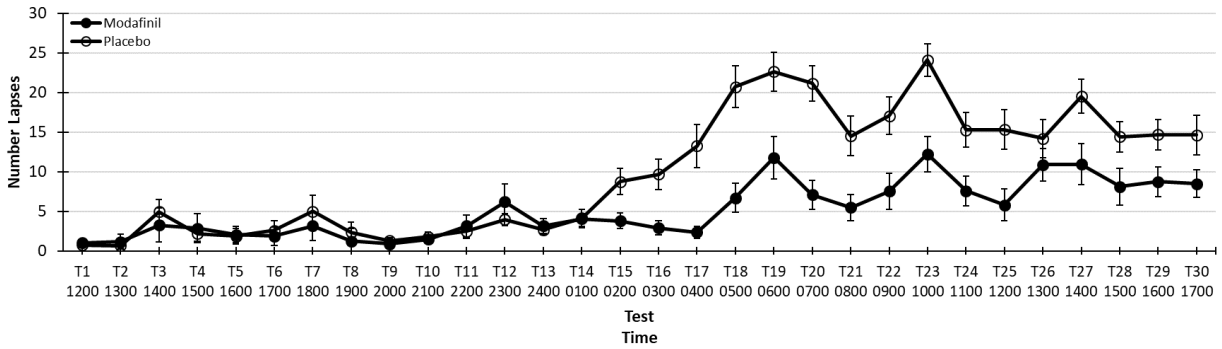


Figure 8. PVT Lapses: Drug by Session Interaction (*M* ± *SE*)

There was a statistically significant main effect for drug ($F(1, 18) = 25.783$, $p < .001$, $\eta_p^2 = .589$) with fewer lapses during the modafinil condition compared to the placebo condition. Means (*SE*) for the modafinil and placebo conditions were 5.195 (0.768) and 9.884 (1.058), respectively.

There was also a statistically significant main effect for session ($F(29, 522) = 27.189$, $p < .001$, $\eta_p^2 = .602$). Within-subjects contrasts revealed significant linear and cubic trends, as well as some higher-order trends. The pattern of responses is shown in Figure 9 below.

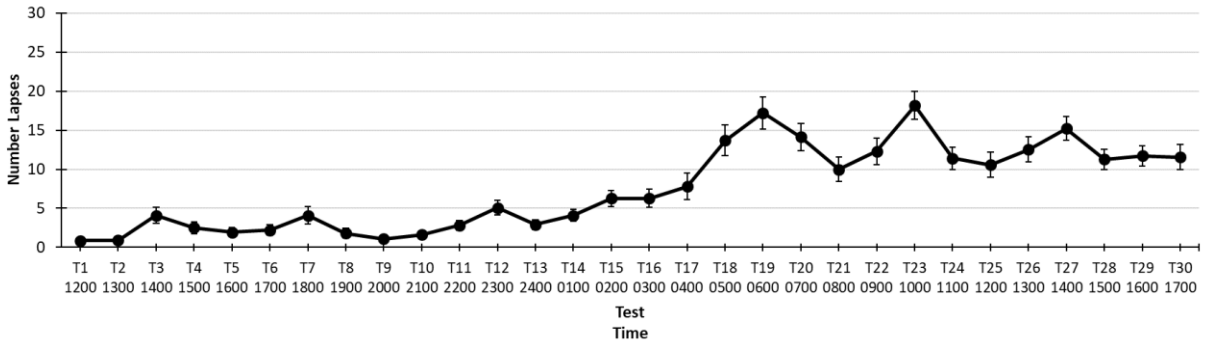


Figure 9. PVT Lapses: Session Main Effect (*M* ± *SE*)

RRT: Due to the number of sessions included in this analysis, Mauchly's Test of Sphericity was not computed; therefore, the assumption of sphericity was assumed. There was a significant interaction between drug and session ($F(29, 522) = 9.152$, $p < .001$, $\eta_p^2 = .337$). Post hoc

analyses indicated differences between the drugs starting at session 15 and continuing throughout the remainder of the sessions (except for session 26), with faster response speed in the modafinil condition than in the placebo condition. The effect is illustrated in Figure 10 below.

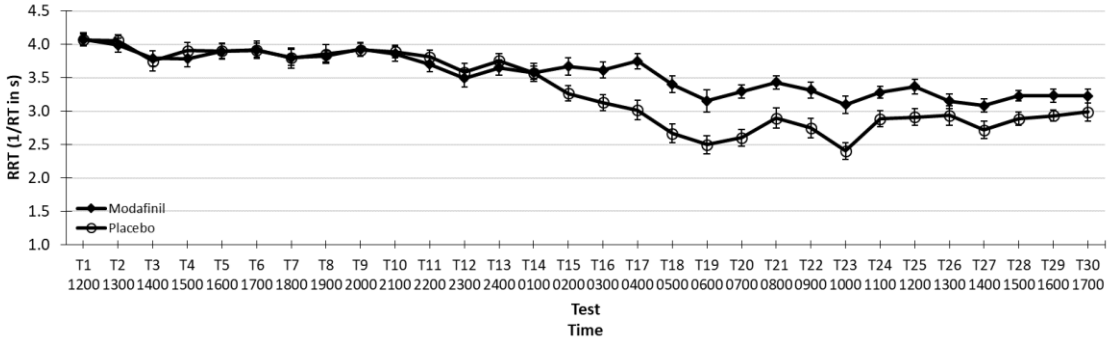


Figure 10. PVT RRT: Drug by Session Interaction ($M \pm SE$)

There was a significant main effect for drug ($F(1,18) = 7.355$, $p = .014$, $\eta_p^2 = .290$) with response speed faster during the modafinil condition than during the placebo condition. Means (*SE*) for the modafinil and placebo conditions were 3.553 (0.092) and 3.310 (0.090), respectively.

There was also a significant main effect for session ($F(29, 522) = 46.465$, $p < .001$, $\eta_p^2 = .721$). Within-subjects contrasts indicated significant linear and cubic trends, as well as several higher order trends. The pattern of responses is shown in Figure 11 below.

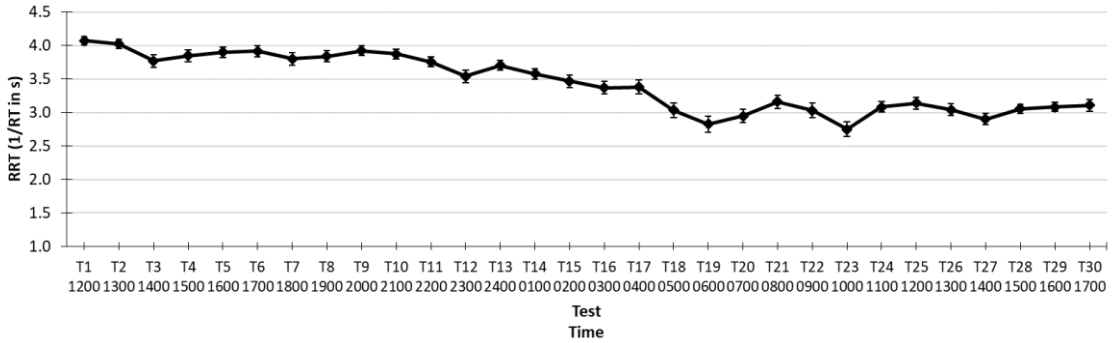


Figure 11. PVT RRT: Session Main Effect ($M \pm SE$)

3.1.1.2 The Stroop Task (NTI ATS™).

The metrics analyzed for the Stroop Task included number of correct responses (NCorr), average RT for number of correct responses (CorrRT), and number of incorrect responses (NIncorr) for each of the congruent, incongruent and neutral stimuli. Additionally, an inhibition index was calculated (incongruent correct RT − neutral correct RT); this index captures when inhibition has been successful relative to neutral trials. One participant scored more than 3 standard deviations from the mean during his baseline session and thus was excluded as an outlier from all analyses, leaving a sample size of 21.

Congruent NCorr: The assumption of sphericity was violated for the drug by session interaction ($\chi^2(9) = 32.934$, $p < .001$, $\varepsilon = .779$). There was a significant drug by session interaction ($F(3.115, 62.292) = 6.952$, $p < .001$, $\eta_p^2 = .258$). Post hoc analyses revealed significant differences between the two drug conditions at sessions 2 through 4, with modafinil showing better performance compared to placebo. Within the modafinil condition, none of the sessions differed from each other. Within the placebo condition, the baseline session and session 1 were significantly better than sessions 2 through 4. Results are shown in Figure 12.

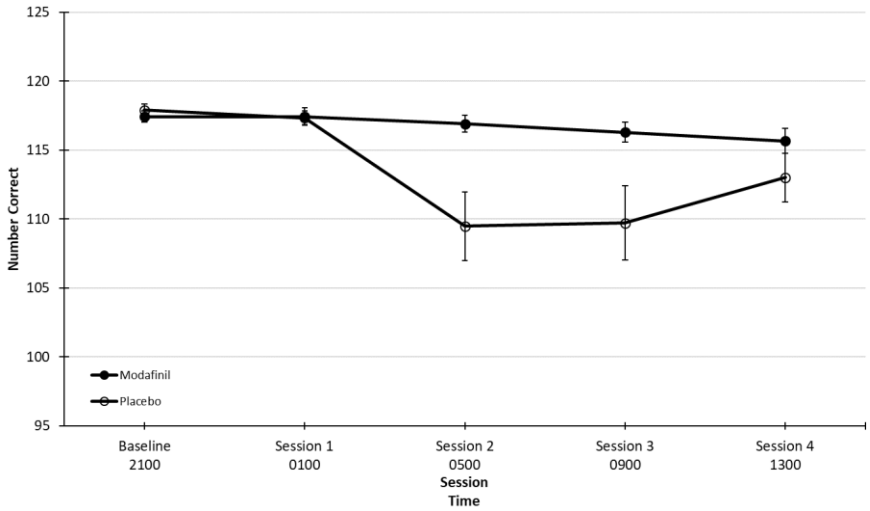


Figure 12. Stroop Task Congruent NCorr: Drug by Session Interaction ($M \pm SE$)

The significant main effect for drug ($F(1, 20) = 18.708$, $p < .001$, $\eta_p^2 = .483$) indicated better overall performance during the modafinil condition than during the placebo condition. The means (SE) for the modafinil and placebo conditions were 58.305 (0.243) and 56.676 (0.441), respectively.

The assumption of sphericity was violated for the session main effect ($\chi^2(9) = 31.365$, $p < .001$, $\varepsilon = .736$). The main effect for session was significant ($F(2.944, 58.879) = 5.155$, $p = .003$, $\eta_p^2 = .205$) and revealed a decline in performance, with the baseline session significantly better than sessions 2 and 3; session 1 was significantly better than sessions 2 through 4; and session 3 was significantly worse than session 4. This pattern of responses is illustrated in Figure 13.

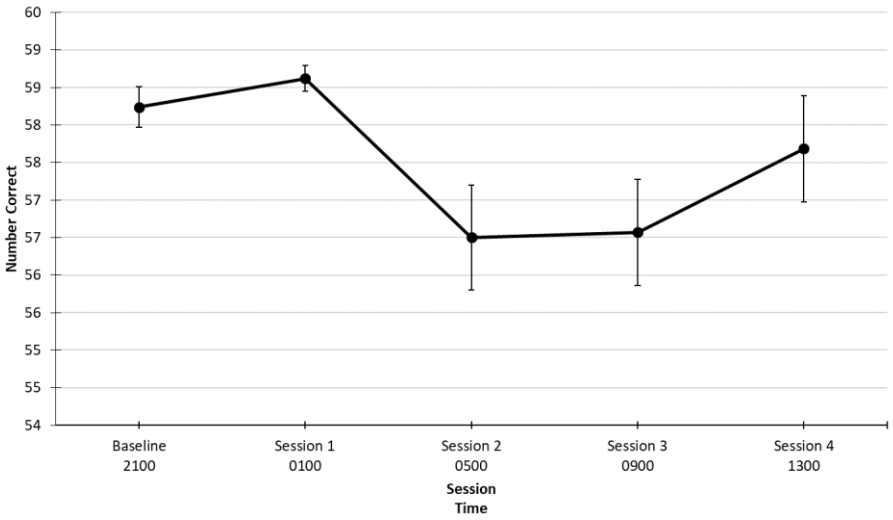


Figure 13. Stroop Task Congruent NCorr: Session Main Effect (*M* ± *SE*)

Congruent CorrRT: The assumption of sphericity was violated for the drug by session interaction ($\chi^2(9) = 34.177$, $p < .001$, $\varepsilon = .519$). There was a significant drug by session interaction ($F(2.075, 41.501) = 3.597$, $p = .035$, $\eta_p^2 = .152$). Post hoc analyses revealed significant differences between the two drug conditions at session 2 and marginally at session 4 ($p = .055$), with modafinil showing faster reaction time compared to placebo. Within the modafinil condition, the baseline session was significantly better than sessions 2 and 3; session 1 was significantly better than sessions 2 through 4. Within the placebo condition, the baseline session was significantly better than sessions 2 through 4; session 1 was significantly better than session 2; and session 2 was significantly worse than sessions 3 and 4. Results are shown in Figure 14.

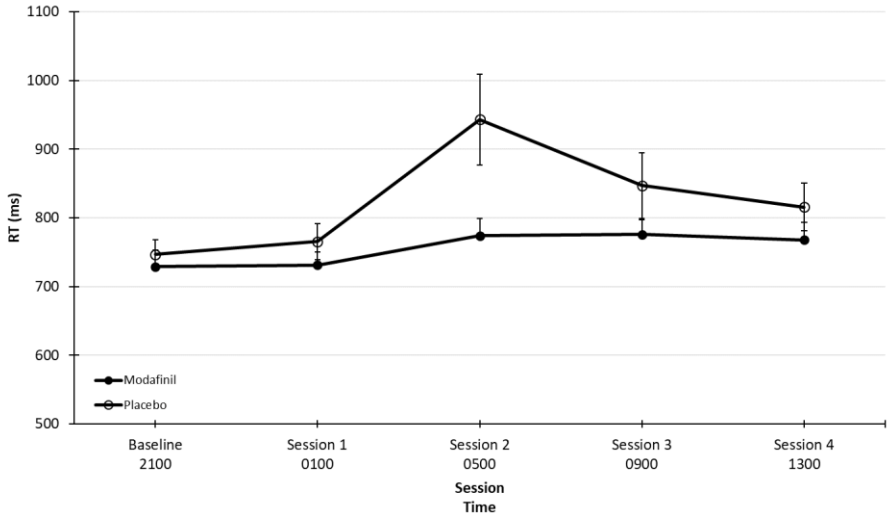


Figure 14. Stroop Task Congruent CorrRT: Drug by Session Interaction (*M* ± *SE*)

The main effect for drug was significant ($F(1, 20) = 11.249$, $p = .003$, $\eta_p^2 = .360$), with faster overall reaction time during the modafinil condition compared to the placebo condition. The

means (*SE*) for the modafinil and placebo conditions were 755.496 (20.621) and 823.595 (33.138), respectively.

The assumption of sphericity was violated for the session main effect ($\chi^2(9) = 34.804$, $p < .001$, $\varepsilon = .623$). The main effect for session was statistically significant ($F(2.492, 49.845) = 9.148$, $p < .001$, $\eta_p^2 = .314$); post hoc analyses revealed significantly faster response times at the baseline session and session 1 compared to sessions 3 and 4; session 2 was significantly slower than all other sessions. This pattern of responses is illustrated in Figure 15.

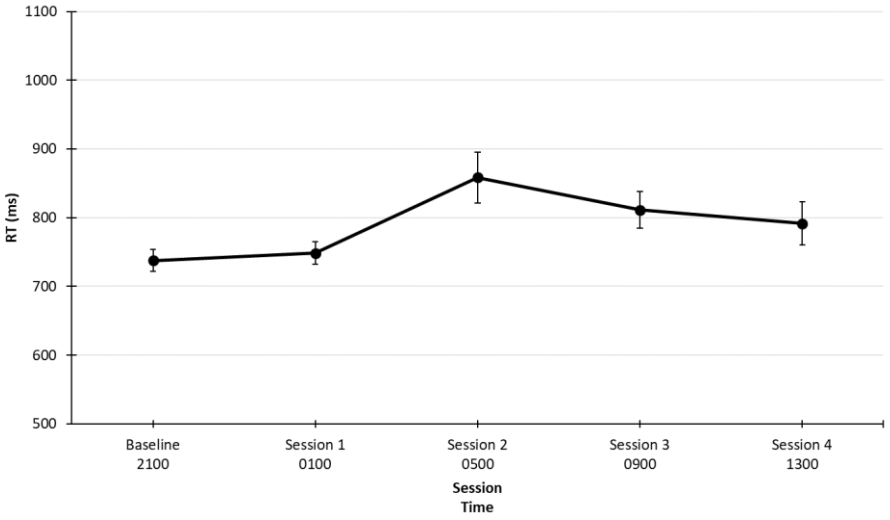


Figure 15. Stroop Task Congruent CorrRT: Session Main Effect ($M \pm SE$)

Congruent Incorr: There was a significant drug by session interaction ($F(4, 80) = 6.009$, $p < .001$, $\eta_p^2 = .231$). Post hoc analyses revealed significant differences between the two drug conditions at sessions 2 through 4, with better performance during the modafinil condition compared to the placebo condition. Within the modafinil condition, none of the sessions were significantly different; however, within the placebo condition, the baseline session and session 1 were significantly better than all other sessions. Results are shown in Figure 16.

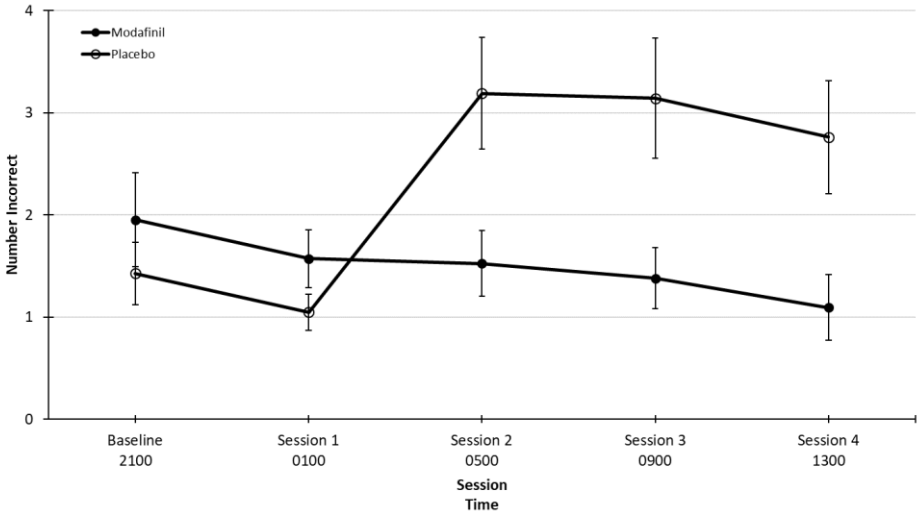


Figure 16. Stroop Task Congruent Incorr: Drug by Session Interaction ($M \pm SE$)

The main effect for drug was significant ($F(1, 20) = 13.902$, $p = .001$, $\eta_p^2 = .410$), indicating better overall performance during the modafinil condition than during the placebo condition. The means (SE) for the modafinil and placebo conditions were 1.505 (0.237) and 2.314 (0.248), respectively.

There was a significant main effect for session ($F(4, 80) = 2.535$, $p = .046$, $\eta_p^2 = .113$). Post hoc comparisons revealed session 1 was significantly better than sessions 2 and 3. This pattern of responses is shown in Figure 17.

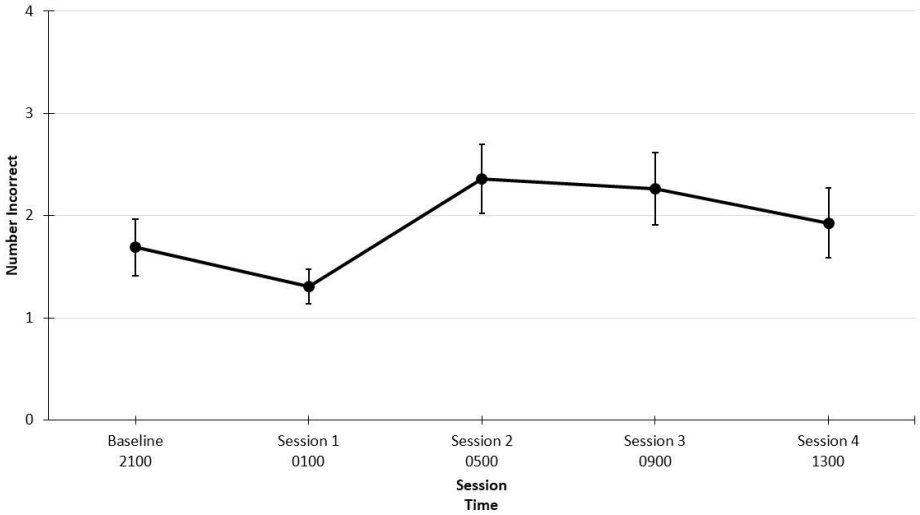


Figure 17. Stroop Task Congruent Incorr: Session Main Effect ($M \pm SE$)

Incongruent NCorr: The assumption of sphericity was violated for the drug by session interaction ($\chi^2(9) = 44.426$, $p < .001$, $\varepsilon = .652$). There was a significant drug by session interaction ($F(2.609, 52.189) = 4.682$, $p = .008$, $\eta_p^2 = .190$). Post hoc analyses revealed significant differences between the two drug conditions at sessions 2 and 3, with better performance during the modafinil

condition compared to placebo. Within the modafinil condition, none of the sessions were statistically different. Within the placebo condition, the baseline session and session 1 were significantly better than sessions 2 through 4; session 3 was significantly worse than session 4. Results are shown in Figure 18.

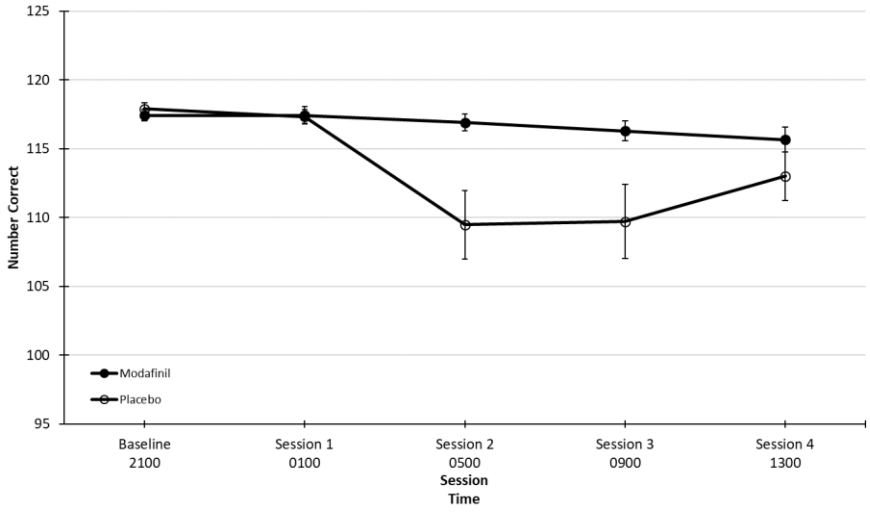


Figure 18. Stroop Task Incongruent NCorr: Drug by Session Interaction ($M \pm SE$)

The main effect for drug was significant ($F(1, 20) = 12.163$, $p = .002$, $\eta_p^2 = .378$) and indicated better overall performance during the modafinil condition than during the placebo condition. The means (SE) for the modafinil and placebo conditions were 116.743 (0.459) and 113.486 (1.120), respectively.

The assumption of sphericity was violated for the session main effect ($\chi^2(9) = 50.658$, $p < .001$, $\varepsilon = .667$). The main effect for session was significant ($F(2.670, 53.400) = 6.502$, $p = .001$, $\eta_p^2 = .245$). The baseline session was significantly better than sessions 2 and 4; session 1 was significantly better than session 2. This pattern is illustrated in Figure 19.

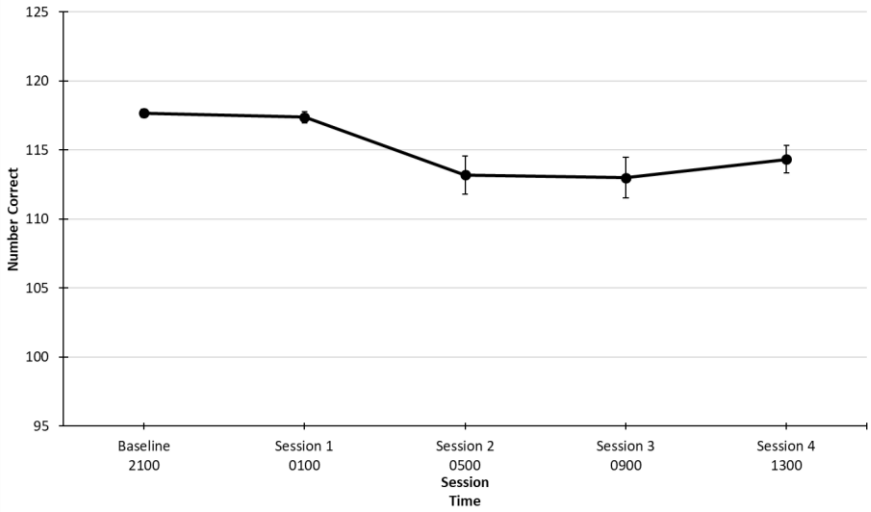


Figure 19. Stroop Task Incongruent NCorr Session Main Effect ($M \pm SE$)

Incongruent CorrRT: The assumption of sphericity was violated for the drug by session interaction ($\chi^2(9) = 19.664$, $p = .021$, $\varepsilon = .844$). There was a significant drug by session interaction ($F(3.377, 67.547) = 6.478$, $p < .001$, $\eta_p^2 = .245$). Post hoc analyses revealed significant differences between the two drug conditions at sessions 2 and 3, with faster reaction times during the modafinil condition compared to placebo. Within the modafinil condition, none of the sessions were significantly different. Within the placebo condition, the baseline session and session 1 were significantly better than sessions 3 and 4; session 2 was significantly worse than the baseline session and sessions 1 and 4. Results are shown in Figure 20.

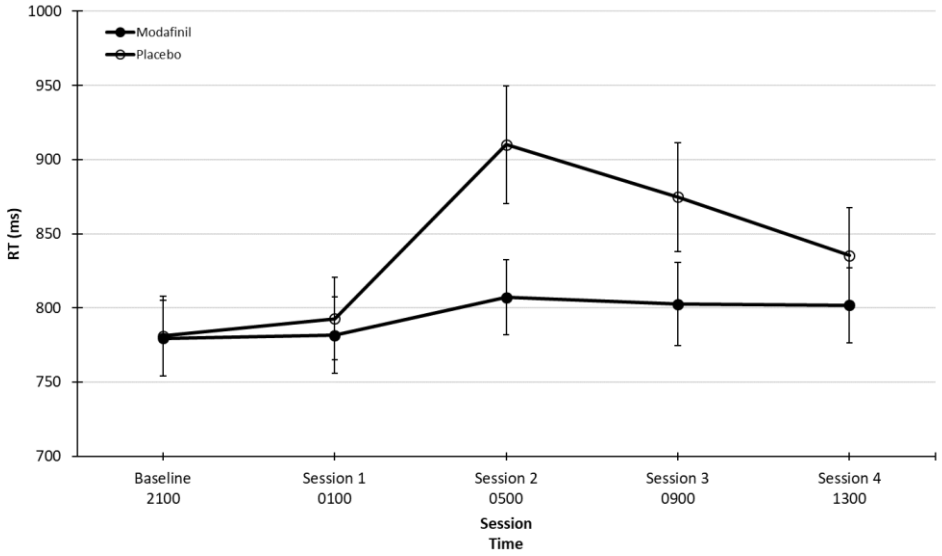


Figure 20. Stroop Task Incongruent CorrRT: Drug by Session Interaction ($M \pm SE$)

The main effect for drug was statistically significant ($F(1, 20) = 8.087$, $p = .010$, $\eta_p^2 = .288$), with response time faster following modafinil than placebo. The means (*SE*) for the modafinil and placebo conditions were 794.590 (24.525) and 838.848 (29.535), respectively.

There was a significant main effect for session ($F(4, 80) = 9.708$, $p < .001$, $\eta_p^2 = .327$). The baseline session and session 1 were significantly faster than sessions 2 through 4; and session 2 was significantly slower than session 4. The pattern of responses is illustrated in Figure 21.

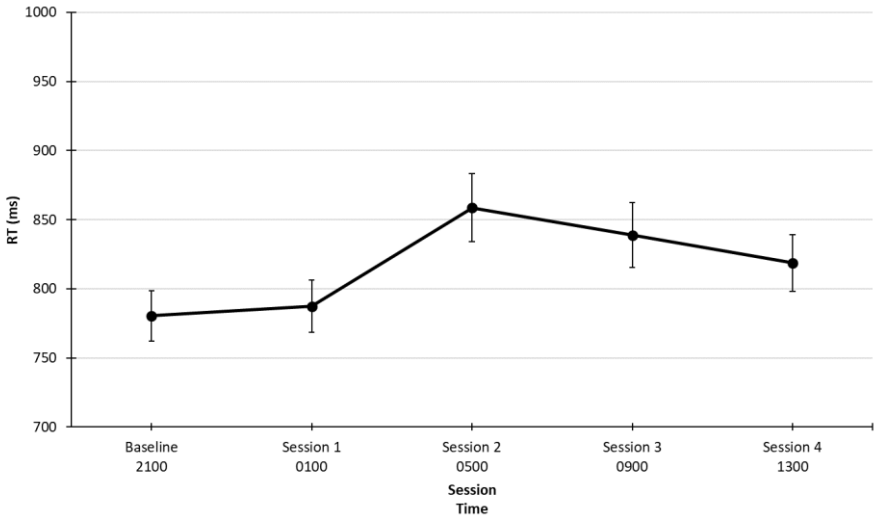


Figure 21. Stroop Task Incongruent CorrRT: Session Main Effect (*M* + *SE*)

Incongruent Incorr: The assumption of sphericity was violated for the drug by session interaction ($\chi^2(9) = 35.990$, $p < .001$, $\varepsilon = .616$). The drug and session interaction approached statistical significance ($F(2.465, 49.306) = 2.857$, $p = .056$, $\eta_p^2 = .125$). Post hoc analyses indicated better performance with modafinil than placebo at sessions 2 and 3. Sessions did not differ within the modafinil condition; however, within the placebo condition, the baseline session showed better performance than sessions 2 through 4, and session 1 showed better performance than sessions 2 and 3. These effects are shown in Figure 22.

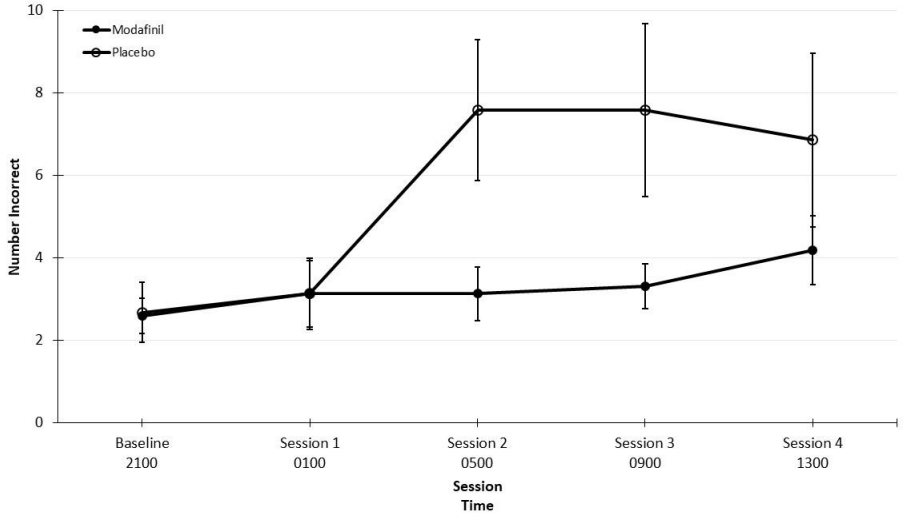


Figure 22. Stroop Task Incongruent Incorr: Drug by Session Interaction ($M \pm SE$)

The main effect for drug was significant ($F(1, 20) = 7.816$, $p = .011$, $\eta_p^2 = .281$), indicating better overall performance during the modafinil condition compared to the placebo condition. The means (*SE*) for the modafinil and placebo conditions were 2.905 (0.420) and 4.467 (0.642), respectively.

The assumption of sphericity was violated for the session main effect ($\chi^2(9) = 39.534$, $p < .001$, $\varepsilon = .696$). There was a significant main effect for session ($F(2.786, 55.719) = 4.927$, $p = .005$, $\eta_p^2 = .198$). The baseline session and session 1 were significantly better than all other sessions; sessions 2 and 3 were significantly worse than all other sessions. The pattern of responses is illustrated in Figure 23.

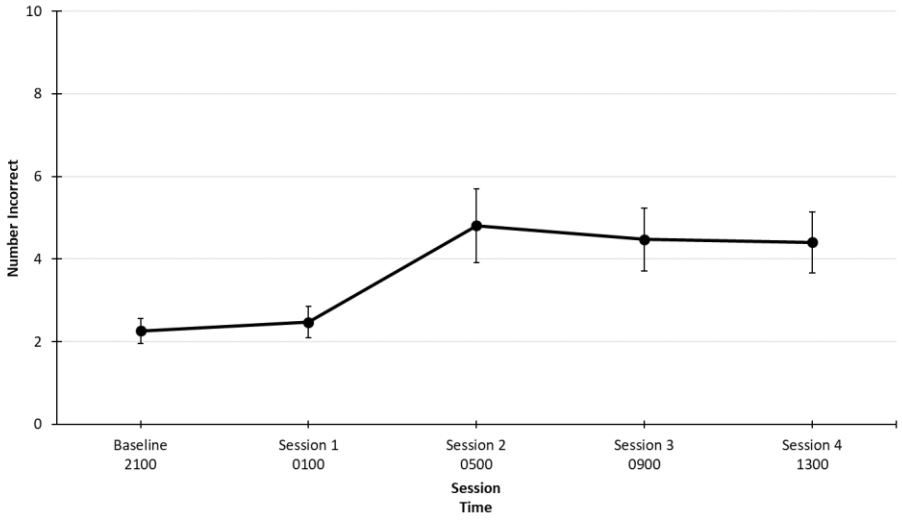


Figure 23. Stroop Task Incongruent Incorr: Session Main Effect ($M \pm SE$)

Neutral NCorr: The assumption of sphericity was violated for the drug by session interaction ($\chi^2(9) = 37.759$, $p < .001$, $\varepsilon = .734$). There was a significant drug by session interaction ($F(2.936, 58.723) = 4.058$, $p = .011$, $\eta_p^2 = .169$). Post hoc analyses revealed significant differences between the two drug conditions at sessions 2 and 3, with modafinil showing better performance at these sessions compared to placebo. Within the modafinil condition, the baseline session was significantly better than session 3, and session 1 was significantly better than sessions 2 through 4. Within the placebo condition, the baseline session and session 1 were significantly better than sessions 2 through 4. Results are shown in Figure 24.

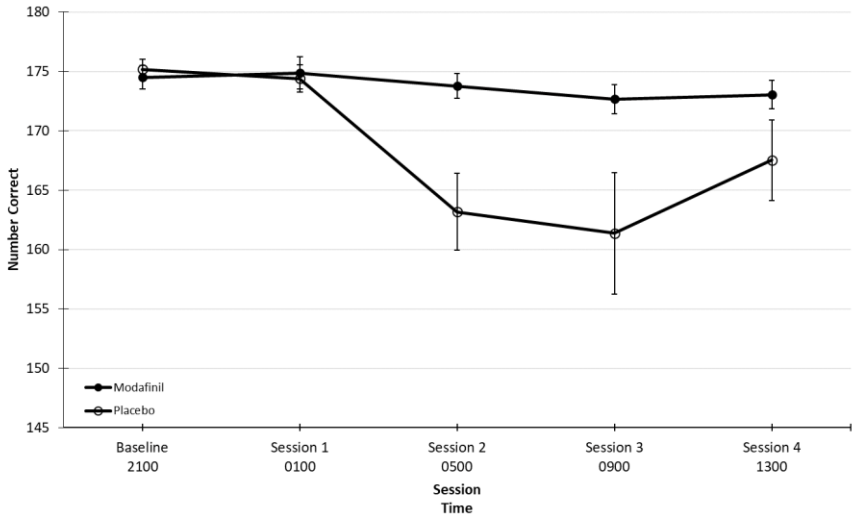


Figure 24. Stroop Task Neutral NCorr: Drug by Session Interaction ($M \pm SE$)

The main effect for drug was significant ($F(1, 20) = 8.998$, $p = .007$, $\eta_p^2 = .310$), indicating better overall performance during the modafinil condition than during the placebo condition. The means (SE) for the modafinil and placebo conditions were 174.190 (0.865) and 169.933 (1.529), respectively.

The assumption of sphericity was violated for the session main effect ($\chi^2(9) = 49.961$, $p < .001$, $\varepsilon = .622$). There was a significant main effect for session ($F(2.487, 49.748) = 6.900$, $p = .001$, $\eta_p^2 = .256$). Post hoc comparisons revealed that the baseline session and session 1 were significantly better than sessions 2 through 4. These effects are shown in Figure 25.

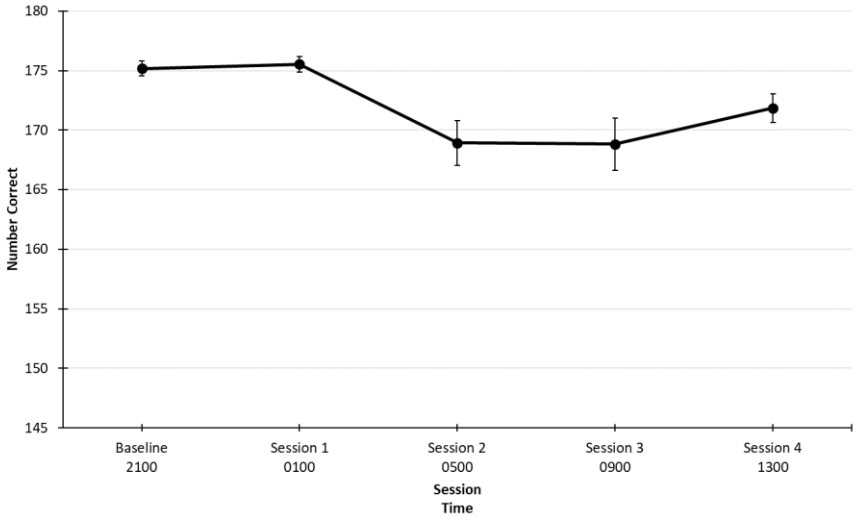


Figure 25. Stroop Task Neutral NCorr: Session Main Effect ($M \pm SE$)

Neutral CorrRT: The assumption of sphericity was violated for the drug by session interaction ($\chi^2(9) = 22.812$, $p = .007$, $\varepsilon = .678$). There was a significant drug by session interaction ($F(3.179,$

63.582) = 4.865, p = .004, η_p^2 = .196). Post hoc analyses revealed significant differences between the two drug conditions at sessions 1 through 3, with faster response time during the modafinil condition compared to placebo. Within the modafinil condition, the baseline session was significantly faster than sessions 1 through 4; session 1 was significantly faster than sessions 2 and 4. Within the placebo condition, the baseline session was significantly faster than sessions 1 through 4; session 1 was significantly faster than session 2 (marginally faster than session 3, p = .054); session 2 was significantly slower than sessions 3 and 4. Results are shown in Figure 26.

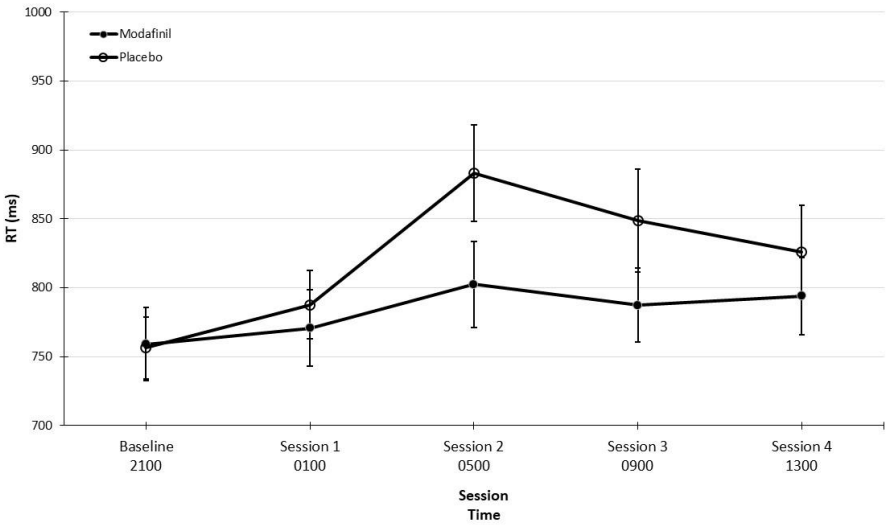


Figure 26. Stroop Task Neutral CorrRT: Drug by Session Interaction ($M \pm SE$)

The main effect for drug was significant (F(1, 20) = 9.448, p = .006, η_p^2 = .321), indicating better overall performance during the modafinil condition than during the placebo condition. The means (*SE*) for the modafinil and placebo conditions were 764.888 (21.005) and 809.484 (27.683), respectively.

The assumption of sphericity was violated for the main effect for session (χ^2(9) = 22.710, p = .007, ε = .714). There was a significant main effect for session (F(3.382, 67.640) = 10.459, p < .001, η_p^2 = .343). Post hoc analyses revealed the baseline session was significantly better than all other sessions; session 1 was significantly better than sessions 2 through 4. The pattern of responses is shown in Figure 27.

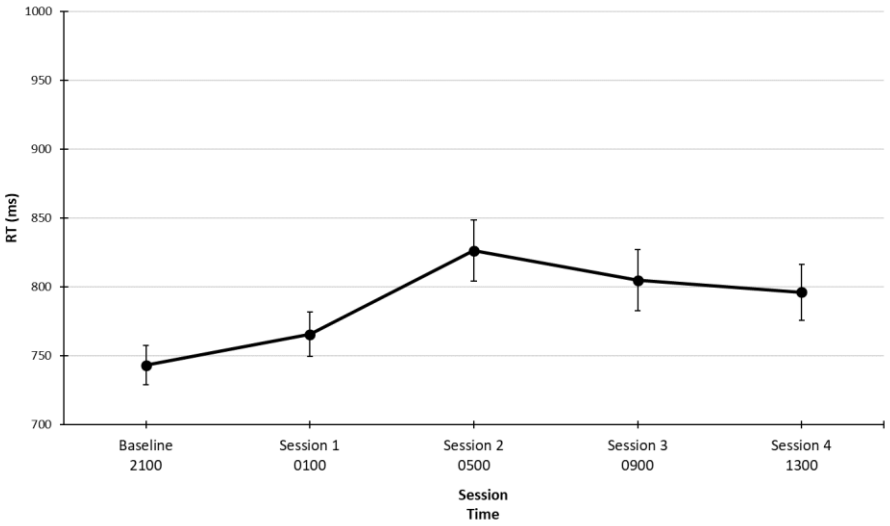


Figure 27. Stroop Task Neutral CorrRT: Session Main Effect ($M \pm SE$)

Neutral Incorr: There was a significant drug by session interaction ($F(4, 80) = 2.628$, $p = .040$, $\eta_p^2 = .116$). Post hoc analyses revealed significant differences between the two drug conditions at session 2, with better performance during the modafinil condition compared to the placebo condition. Within the modafinil condition, session 1 was significantly better than session 3. Within the placebo condition, the baseline session was significantly better than sessions 2 through 4; session 1 was significantly better than session 2. Results are shown in Figure 28.

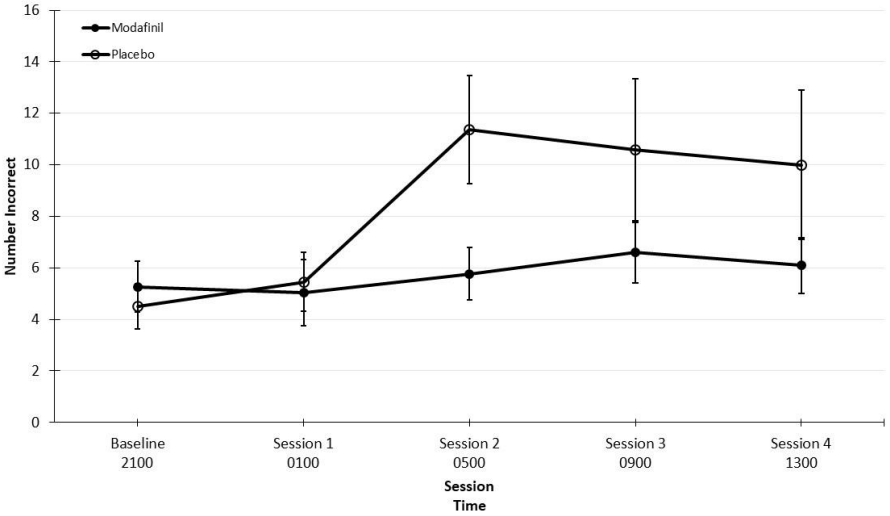


Figure 28. Stroop Task Neutral Incorr: Drug by Session Interaction ($M \pm SE$)

The drug main effect was not statistically significant ($F(1, 20) = 2.943$, $p = .102$, $\eta_p^2 = .128$). The means (SE) for the modafinil and placebo conditions were 5.352 (0.872) and 7.029 (0.907), respectively.

The assumption of sphericity also was violated for the main effect for session ($\chi^2(9) = 36.051$, $p < .001$, $\varepsilon = .577$). The session main effect was significant ($F(2.626, 52.524) = 5.025$, $p = .005$, $\eta_p^2 = .201$). Pairwise comparisons indicated that the baseline session and session 1 were significantly better than sessions 2 through 4. This pattern of responses is illustrated in Figure 29.

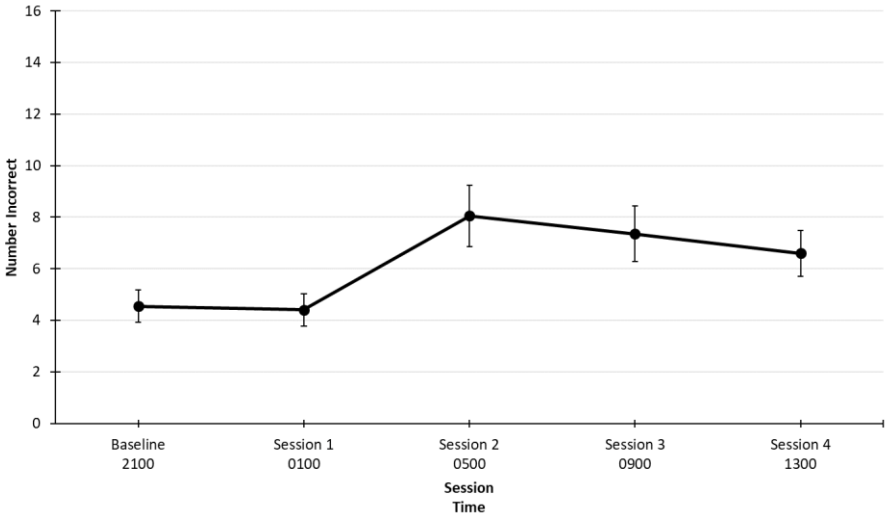


Figure 29. Stroop Task Neutral Incorr: Session Main Effect ($M \pm SE$)

Inhibition Index: There was not a significant drug by session interaction ($F(4, 80) = 2.245$, $p = .071$, $\eta_p^2 = .101$), a significant drug main effect ($F(1, 20) = 0.058$, $p = .813$, $\eta_p^2 = .003$), nor a significant session main effect ($F(4, 80) = 1.410$, $p = .238$, $\eta_p^2 = .066$). The pattern of responses is illustrated in Figure 30.

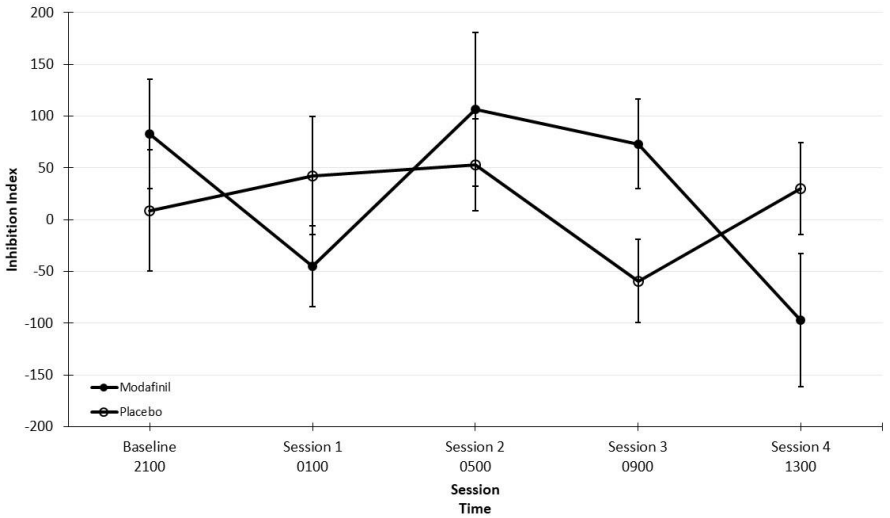


Figure 30. Stroop Task Inhibition Index: Drug by Session Interaction ($M \pm SE$)

3.1.1.3 Rapid Decision Making Task (NTI ATS^{TM}).

The metrics analyzed for the Rapid Decision Making Task included number of correct responses (NCorr) and the average reaction time for the number of correct responses (CorrRT).

NCorr: The assumption of sphericity was violated for the drug by session interaction ($\chi^2(9) = 47.167$, $p < .001$, $\varepsilon = .491$). The interaction between drug and session was not significant ($F(1.966, 41.278) = 2.942$, $p = .065$, $\eta_p^2 = .123$). The responses for the drug by session interaction are shown in Figure 31.

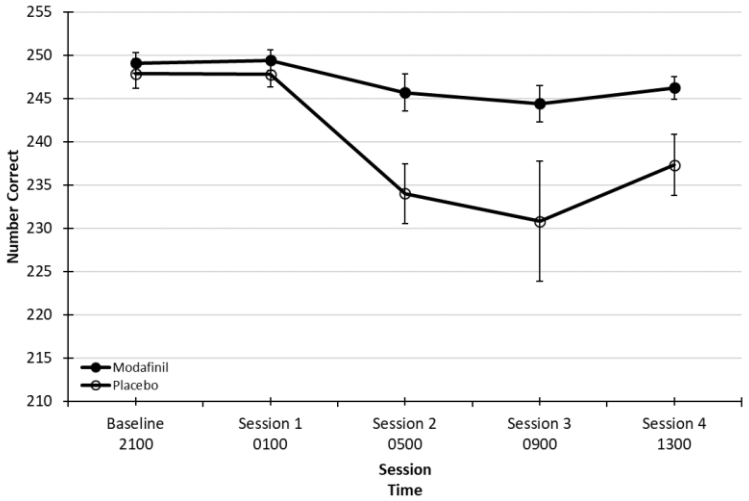


Figure 31. RDMT NCorr: Drug by Session Interaction ($M \pm SE$)

The main effect for drug was significant ($F(1, 21) = 13.171$, $p = .002$, $\eta_p^2 = .385$), indicating better overall performance during the modafinil condition than during the placebo condition. The means (*SE*) for the modafinil and placebo conditions were 246.964 (1.197) and 239.555 (2.363), respectively.

The assumption of sphericity was violated for the session main effect ($\chi^2(9) = 53.981$, $p < .001$, $\varepsilon = .502$). There was a significant main effect for session ($F(2.222, 46.671) = 6.046$, $p = .004$, $\eta_p^2 = .224$). The baseline session and session 1 were significantly better than sessions 2 through 4. This effect is shown in figure 32.

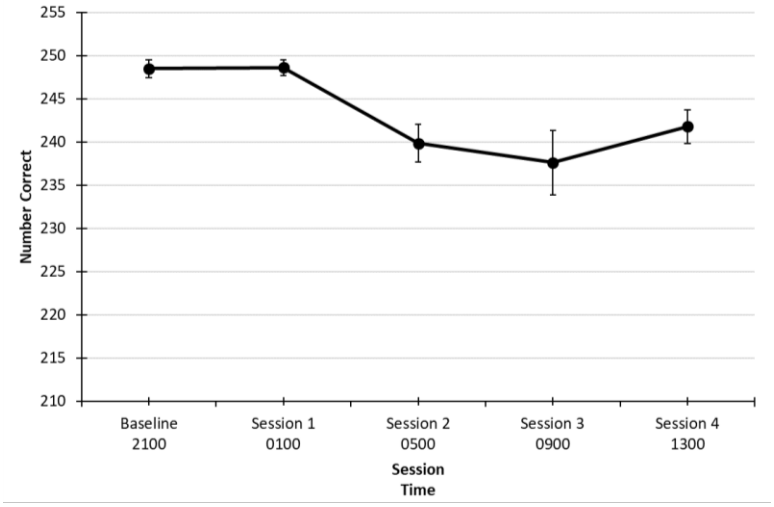


Figure 32. RDMT NCorr: Session Main Effect (*M* ± *SE*)

CorrRT: The assumption of sphericity was violated for the drug by session interaction ($\chi^2(9) = 22.941$, $p = .007$, $\varepsilon = .813$). There was a significant interaction between drug and session ($F(3.252, 68.296) = 6.014$, $p = .001$, $\eta_p^2 = .223$). Post hoc analyses revealed significant differences between the two drug conditions at sessions 1 through 4, with better performance during the modafinil condition compared to placebo. Within the modafinil condition, the baseline session and session 1 were significantly better than sessions 2 through 4. Within the placebo condition, the baseline session was significantly better than sessions 1 through 4; session 1 was significantly better than sessions 2 through 4; session 2 was significantly worse than sessions 3 and 4. Results are shown in Figure 33.

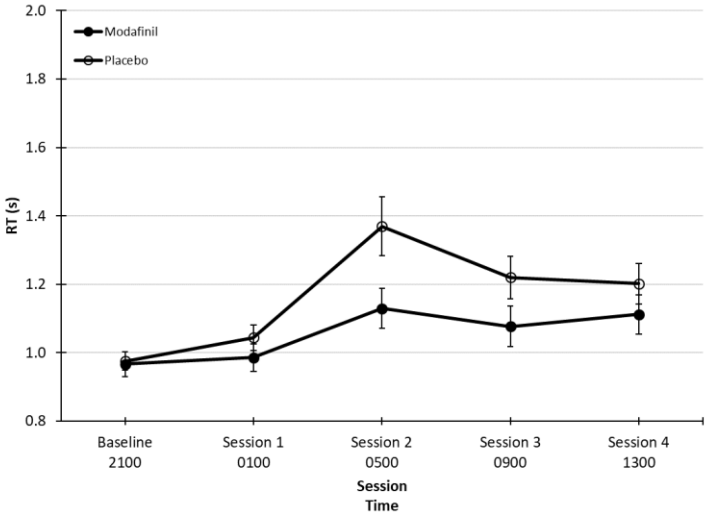


Figure 33. RDMT CorrRT: Drug by Session Interaction (*M* ± *SE*)

The main effect for drug also was significant ($F(1, 21) = 14.054$, $p = .001$, $\eta_p^2 = .401$), indicating better overall performance during the modafinil condition than during the placebo condition. The

means (*SE*) for the modafinil and placebo conditions were 1.054 (0.047) and 1.162 (0.047), respectively.

The assumption of sphericity was violated for the session main effect ($\chi^2(9) = 30.652$, $p < .001$, $\varepsilon = .676$). There was a significant main effect for session ($F(2.702, 56.743) = 20.072$, $p < .001$, $\eta_p^2 = .489$). Pairwise comparisons indicated the baseline session and session 1 were significantly better than sessions 2 through 4; session 2 was significantly worse than sessions 3 and 4. This effect is shown in Figure 34.

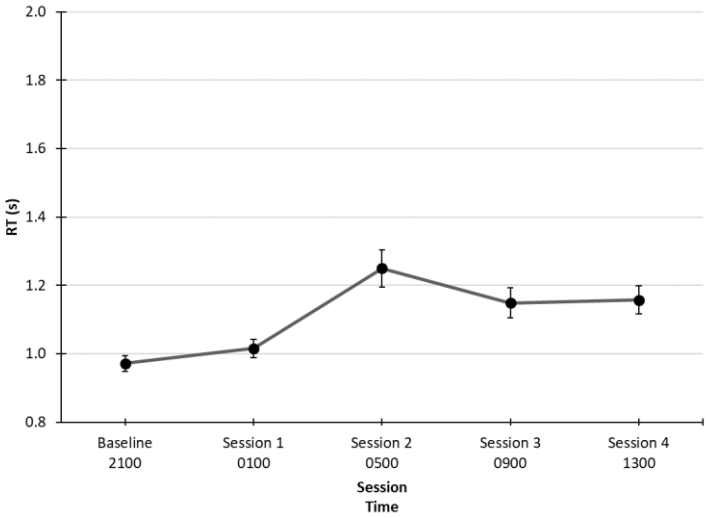


Figure 34. RDMT CorrRT: Session Main Effect (*M* ± *SE*)

3.1.1.4 Delayed Match to Sample Task (DMST) (NTI ATS™).

The metrics analyzed for the Delayed Match to Sample Task (DMST) included number of correct responses (NCorr) and the average reaction time for correct responses (CorrRT).

NCorr: The ANOVA revealed a statistically significant interaction between drug and session ($F(4, 84) = 7.074$, $p < .001$, $\eta_p^2 = .252$). Post hoc analyses indicated significantly better performance during the modafinil condition than during the placebo condition at sessions 2 and 3. For the modafinil condition, the baseline session and session 1 were significantly better than sessions 3 and 4. For the placebo condition, the baseline session was significantly better than sessions 2 through 4; session 1 was significantly better than sessions 2 and 3; and sessions 2 and 3 were significantly worse than session 4. The effects are illustrated in Figure 35.

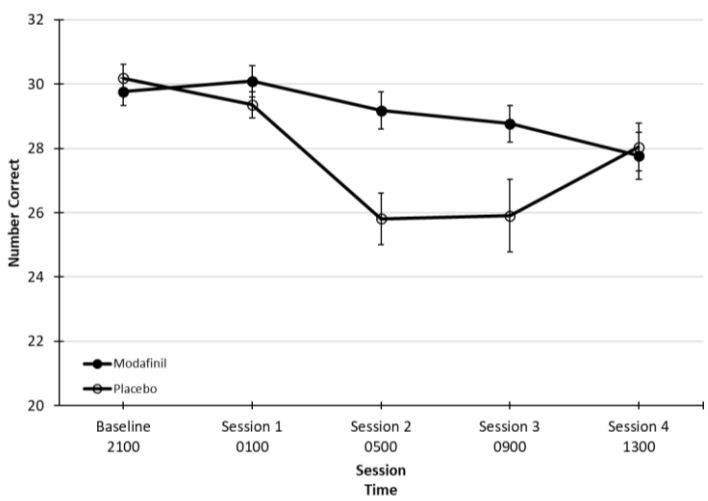


Figure 35. DMTS NCorr: Drug by Session Interaction ($M \pm SE$)

The main effect for drug also was significant ($F(1,21) = 8.980$, $p = .007$, $\eta_p^2 = .300$), indicating better overall performance during the modafinil condition than during the placebo condition. The means (*SE*) for the modafinil and placebo conditions were 29.118 (0.414) and 27.864 (0.542), respectively.

There was a significant main effect for session ($F(4, 84) = 10.292$, $p < .001$, $\eta_p^2 = .329$). The baseline session and session 1 were significantly better than sessions 2 through 4. This effect is shown in Figure 36.

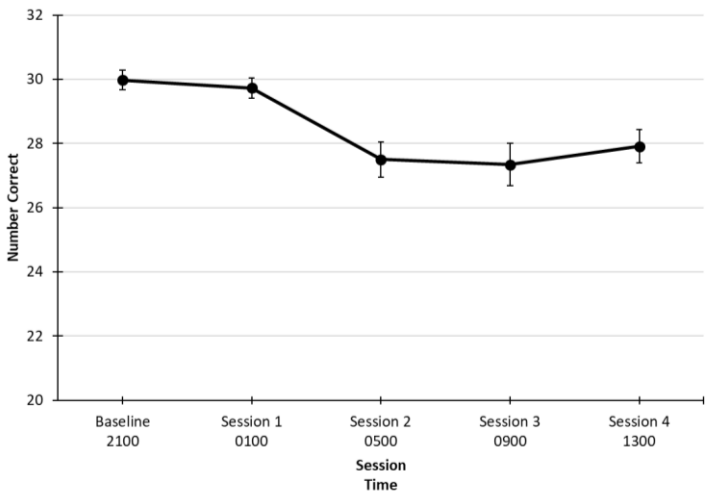


Figure 36. DMTS NCorr: Session Main Effect ($M \pm SE$)

CorrRT: There was not a significant interaction between drug and session ($F(4, 84) = 0.748$, $p = .562$, $\eta_p^2 = .034$). The pattern of responses is illustrated in Figure 37.

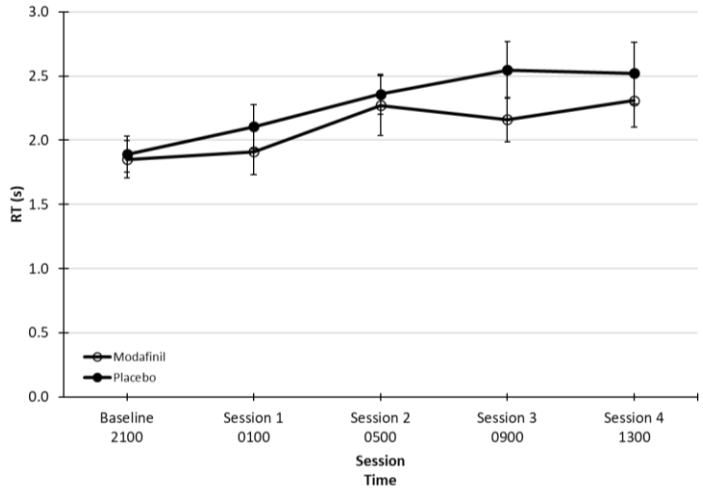


Figure 37. DMTS CorrRT: Drug by Session Interaction ($M \pm SE$)

There also was not a significant main effect for drug ($F(1, 21) = 3.818$, $p = .064$, $\eta_p^2 = .154$). The means (*SE*) for the modafinil and placebo conditions were 2.101 (0.152) and 2.285 (0.153), respectively.

There was a significant main effect for session ($F(4, 84) = 5.739$, $p < .001$, $\eta_p^2 = .215$). The baseline session and session 1 were significantly faster than sessions 2 through 4. These effects are shown in Figure 38.

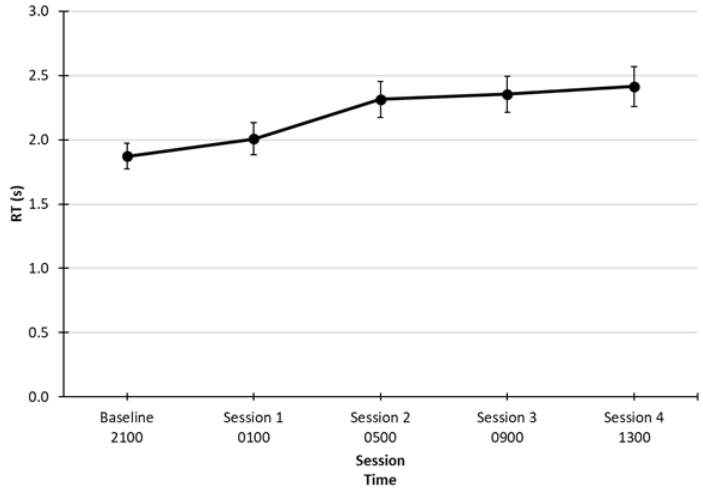


Figure 38. DMTS CorrRT: Session Effect ($M \pm SE$)

3.1.1.5 Wisconsin Card Sorting Task (WCST).

The metrics analyzed for the Wisconsin Card Sorting Task included perseverative errors (PE) and failure to maintain set (FMS).

PE: Mauchly's Test of Sphericity was violated for the drug by session interaction ($\chi^2(9) = 17.074$, $p = .048$, $\varepsilon = .718$). There was not a significant drug by session interaction ($F(3.374, 70.856) = 0.142$, $p = .949$, $\eta_p^2 = .007$), main effect for drug ($F(1, 21) = 0.131$, $p = .721$, $\eta_p^2 = .006$), nor a main effect for session ($F(4, 84) = 0.079$, $p = .988$, $\eta_p^2 = .004$). The pattern of responses is shown in Figure 39.

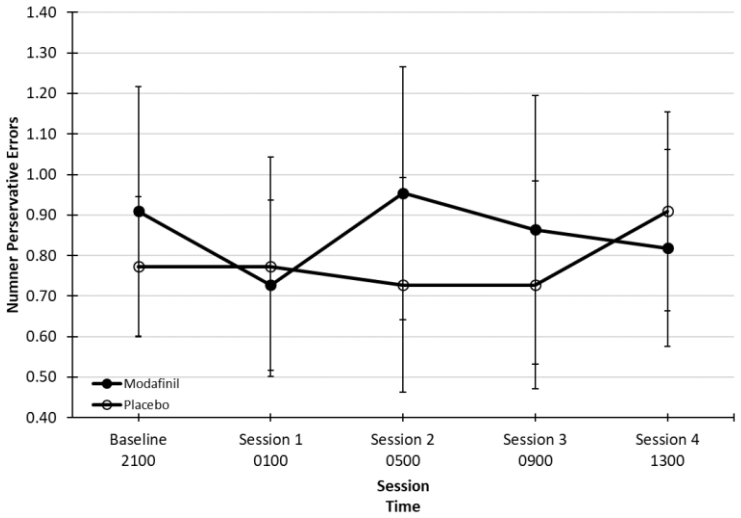


Figure 39. WCST PE: Drug by Session Interaction ($M \pm SE$)

FMS: The repeated measures ANOVA did not show a significant drug by session interaction ($F(4, 84) = 0.303$, $p = .875$, $\eta_p^2 = .014$), main effect of drug ($F(1, 21) = 2.443$, $p = .133$, $\eta_p^2 = .104$), nor a main effect of session ($F(4, 84) = 0.884$, $p = .477$, $\eta_p^2 = .040$). The pattern of responses is shown in Figure 40.

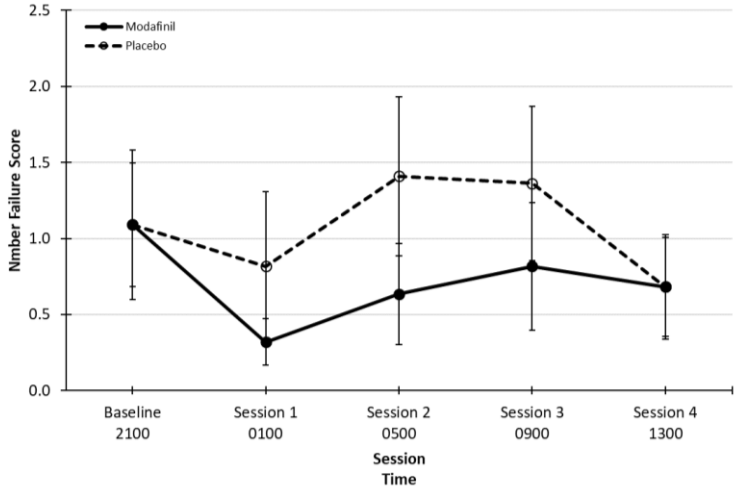


Figure 40. WCST FMS: Drug by Session Interaction ($M \pm SE$)

3.2.1.6 Oculometric assessments.

Due to technical issues with the PMI FIT, 9 participants did not have complete oculometric data, leaving a total sample size of 13. The analyses for the oculometric assessments included amplitude, pupil diameter, constriction latency, and saccadic velocity.

Amplitude: There was not a significant interaction between drug and session ($F(4, 48) = 1.126$, $p = .355$, $\eta_p^2 = .086$). There also was not a significant main effect for drug ($F(1, 12) = 2.412$, $p = .146$, $\eta_p^2 = .167$) nor a significant main effect for session ($F(4, 48) = 0.880$, $p = .483$, $\eta_p^2 = .068$. The pattern of responses is illustrated in Figure 41.

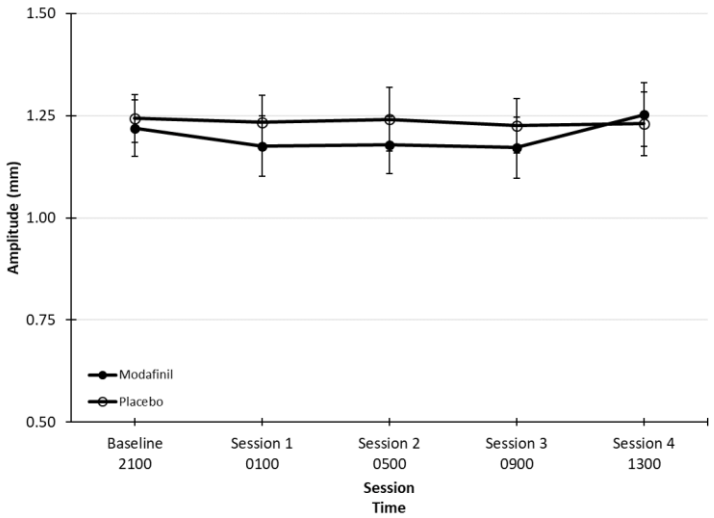


Figure 41. Ocular PMI Amplitude: Drug by Session Interaction ($M \pm SE$)

Pupil diameter: The repeated measures ANOVA did not show a significant interaction between drug and session ($F(4, 48) = 1.157$, $p = .342$, $\eta_p^2 = .088$). There was not a significant main effect for drug ($F(1, 12) = 1.947$, $p = .188$, $\eta_p^2 = .140$) nor a significant main effect for session ($F(4, 48) = 0.371$, $p = .828$, $\eta_p^2 = .030$). Figure 42 illustrates this effect.

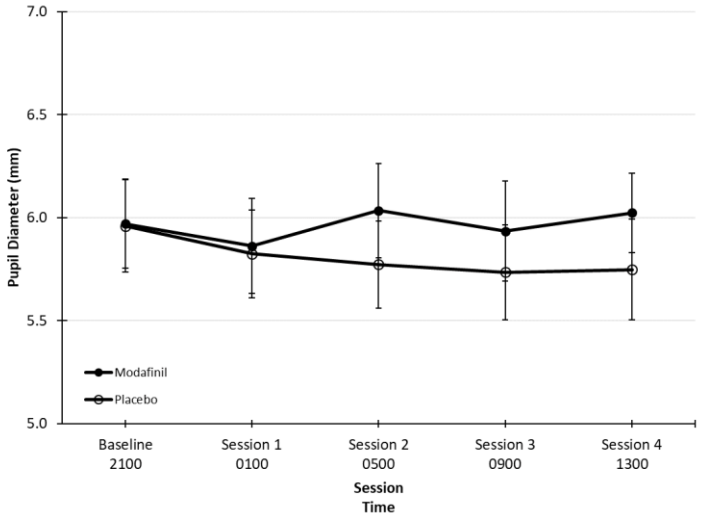


Figure 42. Ocular PMI Pupil Diameter: Drug by Session Interaction ($M \pm SE$)

Constriction latency: The repeated measures ANOVA did not show a significant interaction between drug and session ($F(4, 48) = 0.302$, $p = .875$, $\eta_p^2 = .025$) nor a significant main effect for drug ($F(1, 12) = 0.785$, $p = .393$, $\eta_p^2 = .061$). The pattern of response is illustrated in Figure 43.

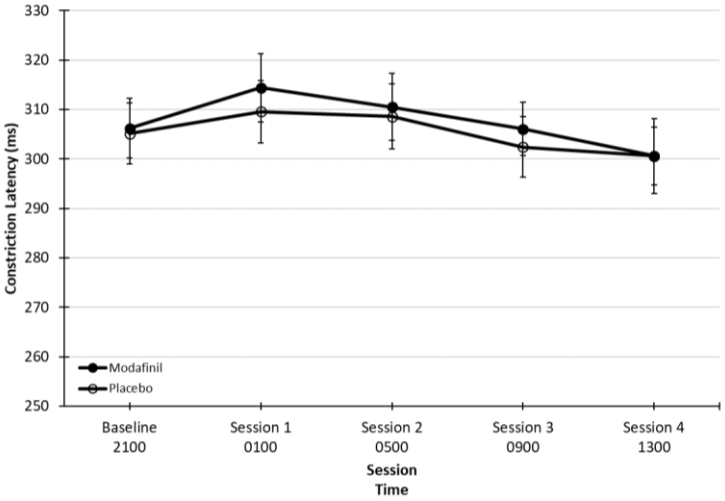


Figure 43. Ocular PMI Constriction Latency: Drug by Session Interaction ($M \pm SE$)

There was a significant main effect for session ($F(4, 48) = 6.329$, $p < .001$, $\eta_p^2 = .345$). Post hoc comparisons indicated that the baseline session had a significantly faster latency than at session 1; session 1 was significantly slower than sessions 3 and 4; and session 2 was significantly slower than session 4. The effect is shown in Figure 44.

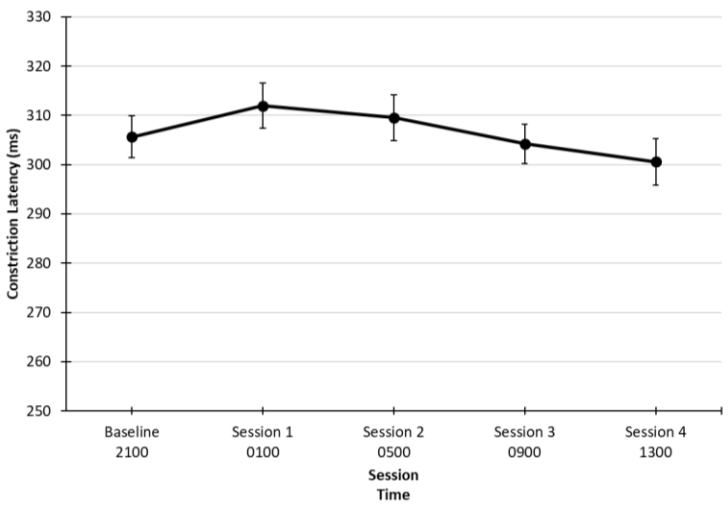


Figure 44. Ocular PMI Constriction Latency: Session Main Effect ($M \pm SE$)

Saccadic velocity: The repeated measures ANOVA did not show a significant interaction between drug and session ($F(4, 48) = 2.250$, $p = .077$, $\eta_p^2 = .158$). There was not a significant main effect for drug ($F(1, 12) = 0.040$, $p = .844$, $\eta_p^2 = .003$). The main effect for session approached statistical significance ($F(4, 48) = 0.713$, $p = .587$, $\eta_p^2 = .056$). The pattern of response is illustrated in Figure 45.

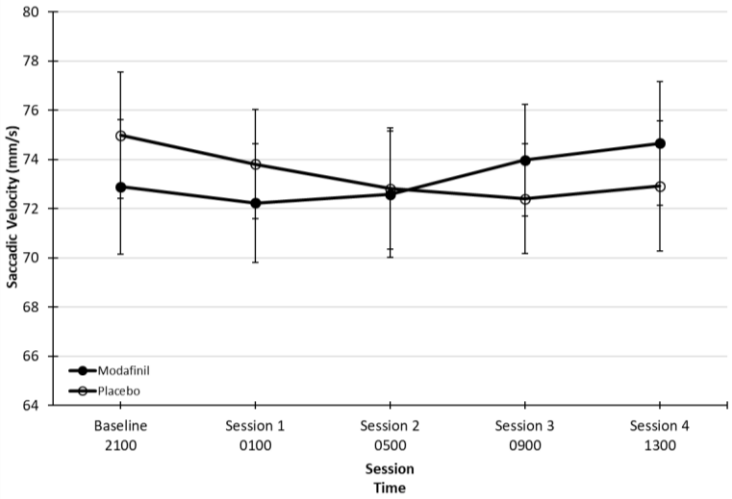


Figure 45. Ocular PMI Saccadic Velocity: Drug by Session Interaction ($M \pm SE$)

3.2.1.7 Contrast visual acuity documented the participant viewing Tumbling "E" optotypes (Taylor, 1977) at a distance of 4 m. The contrast acuity data were sent to collaborators at the U.S. Army Aeromedical Research Laboratory (USAARL). The investigators at USAARL will analyze the data from this test and present the results in a separate report.

3.2.1.8 Resting electroencephalogram (EEG) recordings during eyes closed and eyes open were collected during each session of the study. Preprocessing, artifact removal, and spectral analysis were performed in MathWorks® MATLAB using the FieldTrip toolbox (Donders Institute for

Brain, Cognition, and Behavior). Recordings of the 120-second EEG signal were segmented into 20-s epochs. For the eyes-closed data, artifacts were removed manually. An artifact was defined as a deflection in the frontal poles or ocular channels greater than 75uV occurring in less than 500 ms. For the eyes-open data, blinks and lateral eye movements were removed via independent components analysis (ICA). In some cases, blinks or eye movements occurred relatively infrequently in which case it was deemed preferable to remove them from the trial manually. Further artifacts were removed manually as well. Trials containing less than ~10 seconds of artifact-free data were removed completely. Any participant's data with a single test session containing less than 40 seconds of artifact-free data were removed from further analysis. Three participants were excluded due to insufficient data; six participants were excluded due to excessive blinks, which interfered with the quality of the data. Thus, the sample size for all resting EEG analyses was 13. Data were analyzed via Fast Fourier Transformation with a Hanning taper. Raw frequency data were averaged into delta (0.5 – 4.0 Hz), theta (4.0 – 8.0 Hz), alpha (8.0 – 13.0 Hz), and beta (13.0 – 30.0 Hz) bands, which were converted to percent power by dividing each participant's raw power for each band by the total power (summed from .5 Hz to 30 Hz) and multiplying the quotient by 100. Data obtained during eyes open and eyes closed for each electrode site were analyzed with a three-way ANOVA, with factors of drug (modafinil and placebo), session (BL and sessions 1 through 4), and eyes (open and closed).

Fz-Delta: The assumption of sphericity was violated for the three-way interaction among drug, session, and eyes ($\chi^2(9) = 22.268$, $p = .009$, $\varepsilon = .491$). This interaction was not statistically significant ($F(1.962, 21.566) = 1.241$, $p = .308$, $\eta_p^2 = .101$) nor was the drug by eyes interaction $F(1, 11) = 1.018$, $p = .335$, $\eta_p^2 = .085$).

The assumption of sphericity was violated for the interaction between drug and session ($\chi^2(9) = 37.692$, $p < .001$, $\varepsilon = .379$). The interaction between drug and session was not significant ($F(1.517, 16.684) = 2.207$, $p = .149$, $\eta_p^2 = .167$).

The assumption of sphericity was violated for the interaction between session and eyes ($\chi^2(9) = 36.671$, $p < .001$, $\varepsilon = .367$). This interaction was not significant ($F(1.467, 16.160) = 1.201$, $p = .312$, $\eta_p^2 = .098$).

The main effect of drug was not significant ($F(1, 11) = 3.807$, $p = .077$, $\eta_p^2 = .257$). The means (*SE*) for the modafinil and placebo conditions were 4.709 (0.704) and 6.083 (1.147), respectively.

The assumption of sphericity was violated for the main effect of session ($\chi^2(9) = 33.512$, $p < .001$, $\varepsilon = .546$). The main effect of session was not significant ($F(2.184, 24.028) = 1.559$, $p = .230$, $\eta_p^2 = .124$).

The main effect for eyes was significant ($F(1, 11) = 4.903$, $p = .049$, $\eta_p^2 = .308$); percent power was significantly greater in the eyes-closed condition compared to the eyes-open condition. The means (*SE*) for eyes closed and eyes open were 5.854 (0.931) and 4.936 (0.883), respectively.

Fz-Theta: The assumption of sphericity was violated for the three-way interaction among drug, session, and eyes ($\chi^2(9) = 36.507$, $p < .001$, $\varepsilon = .743$). There was not a significant interaction among drug, session, and eyes ($F(3.481, 35.659) = 1.033$, $p = .389$, $\eta_p^2 = .079$).

The assumption of sphericity was violated for the interaction between drug and session ($\chi^2(9) = 18.092$, $p = .036$, $\varepsilon = .836$). The interaction between drug and session was not significant ($F(3.343, 40.115) = 1.796$, $p = .158$, $\eta_p^2 = .130$), nor was the drug by eyes interaction ($F(1, 12) = .328$, $p = .578$, $\eta_p^2 = .027$).

The assumption of sphericity was violated for the interaction between session and eyes ($\chi^2(9) = 33.479$, $p < .001$, $\varepsilon = .457$). The interaction between session and eyes was not significant ($F(1.828, 21.938) = 1.265$, $p = .299$, $\eta_p^2 = .095$).

The main effect of drug was significant ($F(1, 12) = 6.028$, $p = .030$, $\eta_p^2 = .334$); there was significantly greater percent power in the placebo condition compared to the modafinil condition. The means (*SE*) for the modafinil and placebo conditions were 2.397 (0.583) and 3.057 (0.831), respectively.

The assumption of sphericity was violated for the main effect of session ($\chi^2(9) = 24.311$, $p = .001$, $\varepsilon = .624$). The main effect of session was not significant ($F(2.498, 2.118) = 1.297$, $p = .292$, $\eta_p^2 = .098$) nor was the main effect of eyes ($F(1, 12) = .336$, $p = .573$, $\eta_p^2 = .027$).

FZ-Alpha: The assumption of sphericity was violated for the three-way interaction among drug, session, and eyes ($\chi^2(9) = 24.371$, $p = .004$, $\varepsilon = .770$). The three-way interaction for drug, session, and eyes was not significant ($F(3.079, 33.865) = 1.494$, $p = .233$, $\eta_p^2 = .120$).

The assumption of sphericity was violated for the interaction between drug and session ($\chi^2(9) = 25.703$, $p = .003$, $\varepsilon = .746$). The interaction between drug and session was not significant ($F(2.983, 32.809) = 1.128$, $p = .352$, $\eta_p^2 = .093$).

The interaction between drug and eyes was significant ($F(1, 11) = 5.000$, $p = .047$, $\eta_p^2 = .313$). There were no significant differences between placebo and modafinil within either the eyes-closed or the eyes-open condition nor were there significant differences between eyes-closed or eyes-open during the modafinil condition. However, there were significant differences between eyes-closed and eyes-open during the placebo condition such that power was greater in the eyes-open condition compared to eyes closed. This interaction is illustrated in Figure 46.

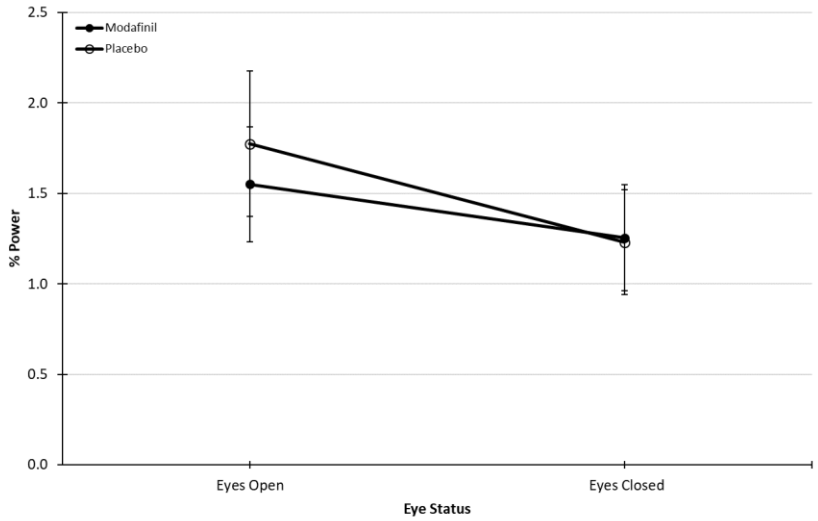


Figure 46. Fz Alpha Percent Power: Drug by Eyes Interaction ($M \pm SE$)

The assumption of sphericity was violated for the interaction between session and eyes ($\chi^2(9) = 32.725$, $p < .001$, $\varepsilon = .439$). The interaction between session and eyes was not significant ($F(1.758, 19.336) = 3.193$, $p = .069$, $\eta_p^2 = .225$).

The main effect of drug was not significant ($F(1, 11) = 1.062$, $p = .325$, $\eta_p^2 = .088$). The means (*SE*) for the modafinil and placebo conditions were 1.403 (0.294) and 1.502 (0.337), respectively.

The main effect of eyes was significant ($F(1, 11) = 5.859$, $p = .034$, $\eta_p^2 = .348$); there was significantly greater percent power during the eyes-open condition compared to the eyes-closed condition. The means (*SE*) for the eyes-open and eyes-closed conditions were 1.662 (0.356) and 1.243 (0.289), respectively.

The assumption of sphericity was violated for the main effect of session ($\chi^2(9) = 30.209$, $p < .001$, $\varepsilon = .458$). The main effect of session was significant ($F(1.831, 20.140) = 7.129$, $p = .005$, $\eta_p^2 = .393$). The baseline session and session 1 had significantly greater percent power compared to sessions 2 through 4; session 2 had significantly greater power than session 3. This effect is illustrated in Figure 47.

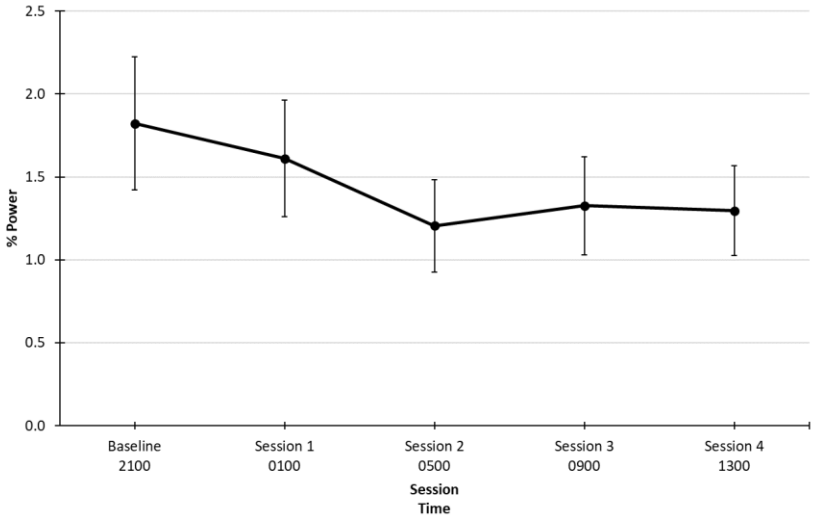


Figure 47. Fz Alpha Percent Power: Session Main Effect ($M \pm SE$)

FZ-Beta: The assumption of sphericity was violated for the three-way interaction among drug, session, and eyes ($\chi^2(9) = 22.167$, $p = .009$, $\varepsilon = .727$). The three-way interaction for drug, session, and eyes was not significant ($F(2.907, 34.878) = 2.401$, $p = .086$, $\eta_p^2 = .167$).

The assumption of sphericity was violated for the interaction between drug and session ($\chi^2(9) = 23.946$, $p = .005$, $\varepsilon = .564$). The interaction between drug and session was not significant ($F(2.258, 27.094) = 0.520$, $p = .622$, $\eta_p^2 = .059$).

The interaction between drug and eyes was significant ($F(1, 11) = 8.423$, $p = .014$, $\eta_p^2 = .434$). Within the eyes-closed condition, there were no significant differences between placebo and modafinil. Within the eyes-open condition, there were significant differences such that percent power was greater during the placebo condition compared to the modafinil condition. Percent power was greater in the eyes-open condition compared to the eyes-closed condition within both the placebo and modafinil condition. This interaction is illustrated in Figure 48.

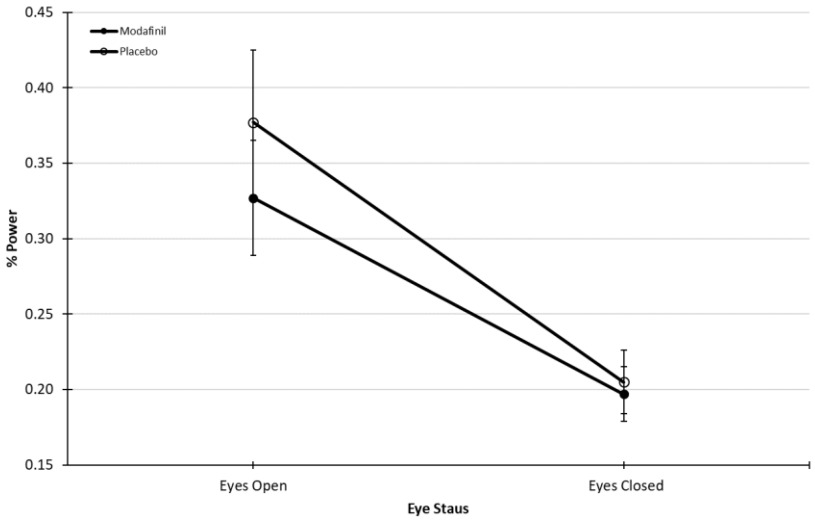


Figure 48. Fz Beta Percent Power: Drug by Eyes Interaction ($M \pm SE$)

The assumption of sphericity was violated for the interaction between session and eyes ($\chi^2(9) = 44.492$, $p < .001$, $\varepsilon = .428$). The interaction between session and eyes was not significant ($F(2.703, 32.436) = 1.408$, $p = .259$, $\eta_p^2 = .042$).

The main effect of drug was not significant ($F(1, 12) = 0.592$, $p = .456$, $\eta_p^2 = .047$). The means (*SE*) for the modafinil and placebo conditions were 0.262 (0.028) and 0.291 (0.034), respectively.

The main effect of eyes was not significant ($F(1, 12) = 4.942$, $p = .046$, $\eta_p^2 = .292$). The means (*SE*) for the eyes-open and eyes-closed conditions were 0.201 (0.019) and 0.352 (0.042), respectively.

The assumption of sphericity was violated for the main effect of session ($\chi^2(9) = 25.623$, $p = .003$, $\varepsilon = .759$). The main effect of session was significant ($F(3.037, 36.440) = 5.675$, $p = .003$, $\eta_p^2 = .321$). Post-hoc analyses indicate that percent power was greater during the baseline session compared to sessions 2 through 4; session 1 percent power was significantly greater than session 2. This interaction is illustrated in Figure 49.

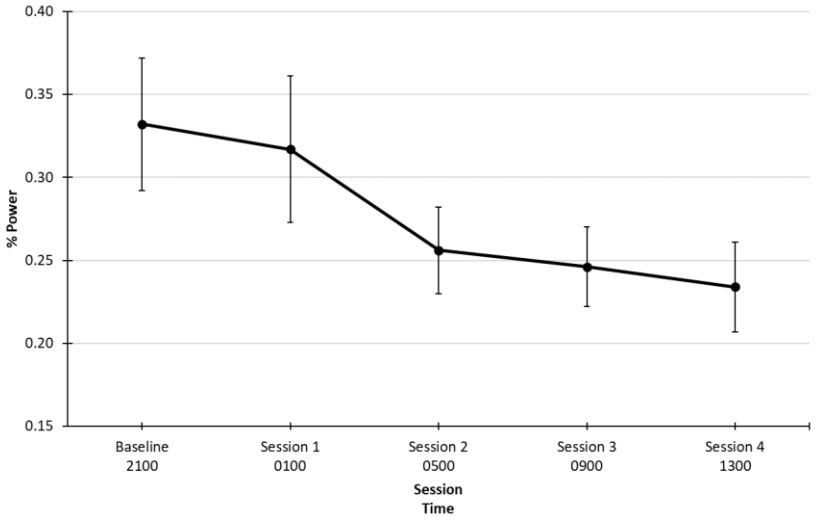


Figure 49. Fz Beta Percent Power: Session Main Effect ($M \pm SE$)

CZ-Delta: There was not a significant drug by session by eyes interaction ($F(4, 48) = 0.762$, $p = .579$, $\eta_p^2 = .057$), drug by session interaction ($F(4, 48) = 2.338$, $p = .069$, $\eta_p^2 = .163$), drug by eyes interaction ($F(1, 12) = 0.788$, $p = .392$, $\eta_p^2 = .062$), nor session by eyes interaction ($F(4, 48) = 0.946$, $p = .446$, $\eta_p^2 = .073$).

The main effect of drug ($F(1, 12) = 5.146$, $p = .043$, $\eta_p^2 = .300$) was significant; percent power was significantly greater during the placebo condition than during the modafinil condition. The means (*SE*) for the placebo and modafinil conditions were 5.387 (0.714) and 4.840 (0.651), respectively.

The assumption of sphericity was violated for the main effect of session ($\chi^2(9) = 40.685$, $p < .001$, $\varepsilon = .399$). The main effect of session was not significant ($F(1.598, 19.174) = 1.328$, $p = .282$, $\eta_p^2 = .100$).

The main effect of eyes was not significant ($F(1, 12) = 2.231$, $p = .161$, $\eta_p^2 = .157$). The means (*SE*) for the eyes closed and eyes open conditions were 5.409 (0.728) and 4.818 (0.673), respectively.

CZ-Theta: The assumption of sphericity was violated for the three-way interaction among drug, session, and eyes ($\chi^2(9) = 36.763$, $p < .001$, $\varepsilon = .580$). The three-way interaction for drug, session, and eyes was not significant ($F(2.319, 27.833) = 1.354$, $p = .277$, $\eta_p^2 = .101$).

The assumption of sphericity was violated for the interaction between drug and session ($\chi^2(9) = 23.123$, $p = .007$, $\varepsilon = .779$). The interaction between drug and session was not significant ($F(3.114, 37.371) = 1.862$, $p = .151$, $\eta_p^2 = .134$), nor was the interaction between drug and eyes ($F(1, 12) = 0.803$, $p = .388$, $\eta_p^2 = .063$).

The assumption of sphericity was violated for the interaction between session and eyes ($\chi^2(9) = 53.021$, $p < .001$, $\varepsilon = .355$). The interaction between session and eyes was not significant ($F(1.420, 17.044) = 0.248$, $p = .708$, $\eta_p^2 = .134$).

The main effect of drug was significant ($F(1, 12) = 0.5.101$, $p = .043$, $\eta_p^2 = .298$); there was significantly greater percent power during the placebo condition than during the modafinil condition. The means (*SE*) for the modafinil and placebo conditions were 3.476 (1.013) and 2.835 (0.782).

Neither the main effect of session ($F(4, 48) = 0.719$, $p = .583$, $\eta_p^2 = .057$) nor the main effect of eyes ($F(1, 12) = 0.061$, $p = .809$, $\eta_p^2 = .005$) were significant. The means (*SE*) for the eyes closed and eyes open conditions were 3.229 (0.927) and 3.081 (0.957), respectively.

CZ-Alpha: The assumption of sphericity was violated for the three-way interaction among drug, session, and eyes ($\chi^2(9) = 22.167$, $p = .009$, $\varepsilon = .727$). There was no significant drug by session by eyes interaction ($F(2.907, 34.878) = 2.401$, $p = .086$, $\eta_p^2 = .167$), nor a significant drug by eyes interaction ($F(1, 12) = .942$, $p = .351$, $\eta_p^2 = .073$).

The assumption of sphericity was violated for the interaction between drug and session ($\chi^2(9) = 23.946$, $p = .005$, $\varepsilon = .564$). The interaction between drug and session was not significant ($F(2.258, 27.094) = 0.520$, $p = .622$, $\eta_p^2 = .059$).

The assumption of sphericity was violated for the interaction between session and eyes ($\chi^2(9) = 44.492$, $p < .001$, $\varepsilon = .428$). The interaction between session and eyes was not significant ($F(2.703, 32.436) = 1.408$, $p = .259$, $\eta_p^2 = .042$).

The main effect of drug was not significant ($F(1, 12) = 0.592$, $p = .456$, $\eta_p^2 = .047$). The means (*SE*) for the modafinil and placebo conditions were 2.248 (0.781) and 2.303 (0.795), respectively.

The main effect of eyes was not significant ($F(1, 12) = 4.942$, $p = .046$, $\eta_p^2 = .292$). The means (*SE*) for the eyes closed and eyes open conditions were 2.120 (0.781) and 2.431 (0.799), respectively.

The assumption of sphericity was violated for the main effect of session ($\chi^2(9) = 25.623$, $p = .003$, $\varepsilon = .759$). The main effect of session was significant ($F(3.037, 36.440) = 5.675$, $p = .003$, $\eta_p^2 = .321$). Post-hoc analyses indicated that the baseline session had significantly greater percent power than sessions 2 through 4; session 1 had significantly greater power than session 2. This effect is illustrated in Figure 50.

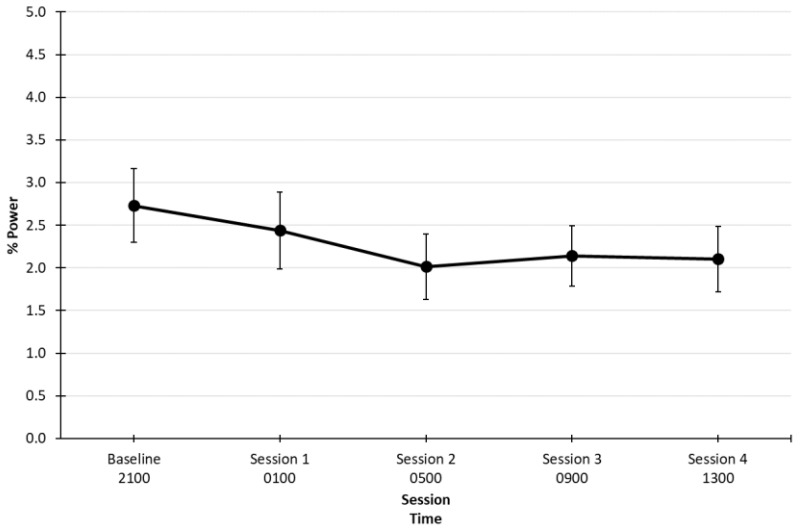


Figure 50. Cz Alpha Percent Power: Session Main Effect ($M \pm SE$)

CZ-Beta: The assumption of sphericity was violated for the three-way interaction among drug, session, and eyes ($\chi^2(9) = 22.167$, $p = .009$, $\varepsilon = .727$). The three-way interaction among drug, session, and eyes was not significant ($F(2.907, 34.878) = 2.401$, $p = .086$, $\eta_p^2 = .167$).

The assumption of sphericity was violated for the interaction between drug and session ($\chi^2(9) = 23.946$, $p = .005$, $\varepsilon = .564$). There was no drug by session interaction ($F(2.258, 27.094) = 0.520$, $p = .622$, $\eta_p^2 = .059$), nor a drug by eyes interaction ($F(1, 11) = .692$, $p = .423$, $\eta_p^2 = .059$).

The assumption of sphericity was violated for the interaction between session and eyes ($\chi^2(9) = 44.492$, $p < .001$, $\varepsilon = .428$). The interaction between session and eyes was not significant ($F(2.703, 32.436) = 1.408$, $p = .259$, $\eta_p^2 = .042$).

The main effect of drug was not significant ($F(1, 12) = 0.592$, $p = .456$, $\eta_p^2 = .047$). The means (*SE*) for the modafinil and placebo conditions were 0.279 (0.044) and 0.295 (0.050), respectively.

The main effect of eyes was not significant ($F(1, 12) = 4.942$, $p = .046$, $\eta_p^2 = .292$). The means (*SE*) for the eye closed and eyes open conditions were 0.240 (0.037) and 0.334 (0.058), respectively.

The assumption of sphericity was violated for the main effect of session ($\chi^2(9) = 25.623$, $p = .003$, $\varepsilon = .759$). The main effect of session was significant ($F(3.037, 36.440) = 5.675$, $p = .003$, $\eta_p^2 = .321$). Post-hoc analyses indicate that the baseline session had significantly greater power than sessions 2 through 4; session 1 had significantly greater power than session 2. This effect is illustrated in Figure 51.

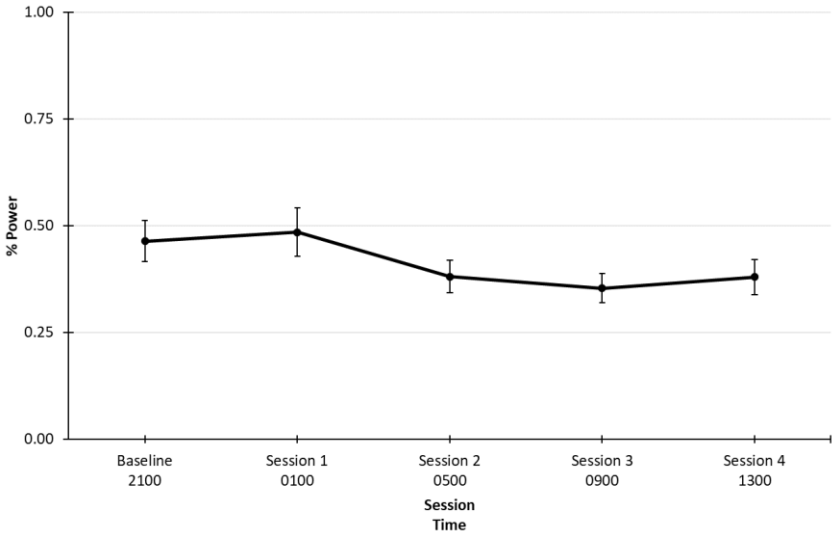


Figure 51. Cz Beta Percent Power: Session Main Effect ($M \pm SE$)

PZ-Delta: The assumption of sphericity was violated for the three-way interaction among drug, session, and eyes ($\chi^2(9) = 25.909$, $p = .002$, $\varepsilon = .549$). The three-way interaction among drug, session, and eyes was not significant ($F(2.195, 26.344) = 0.905$, $p = .425$, $\eta_p^2 = .070$).

The assumption of sphericity was violated for the interaction between drug and session ($\chi^2(9) = 73.946$, $p < .001$, $\varepsilon = .307$). There was no significant drug by session interaction ($F(1.229, 14.744) = 0.727$, $p = .435$, $\eta_p^2 = .057$), nor a drug by eyes interaction ($F(1, 12) = .534$, $p = .479$, $\eta_p^2 = .043$).

The assumption of sphericity was violated for the interaction between eyes and session ($\chi^2(9) = 22.734$, $p = .007$, $\varepsilon = .604$). The interaction between eyes and session was not significant ($F(2.414, 28.971) = 1.026$, $p = .383$, $\eta_p^2 = .079$).

The main effect of drug was not significant ($F(1, 12) = .774$, $p = .396$, $\eta_p^2 = .061$). The means (*SE*) for the modafinil and placebo conditions were 5.313 (1.216) and 4.418 (0.471), respectively.

The main effect of eyes was not significant ($F(1, 12) = .710$, $p = .416$, $\eta_p^2 = .056$). The means (*SE*) for the eyes closed and eyes open conditions were 4.683 (0.668) and 5.049 (0.911), respectively.

The assumption of sphericity was violated for the main effect of session ($\chi^2(9) = 81.690$, $p < .001$, $\varepsilon = .287$). The main effect of session was not significant ($F(1.150, 13.794) = 0.188$, $p = .706$, $\eta_p^2 = .015$).

PZ-Theta: The assumption of sphericity was violated for the three-way interaction among drug, session, and eyes ($\chi^2(9) = 24.699$, $p = .004$, $\varepsilon = .821$). The three-way interaction among drug, session, and eyes was not significant ($F(7.088, 39.410) = 1.250$, $p = .306$, $\eta_p^2 = .094$).

The assumption of sphericity was violated for the interaction between drug and session ($\chi^2(9) = 49.256$, $p < .001$, $\varepsilon = .619$). There was no significant drug by session interaction ($F(2.475, 29.697) = 1.172$, $p = .331$, $\eta_p^2 = .089$), nor a drug by eyes interaction ($F(1, 12) = 0.601$, $p = .453$, $\eta_p^2 = .048$).

The assumption of sphericity was violated for the interaction between session and eyes ($\chi^2(9) = 39.252$, $p < .001$, $\varepsilon = .484$). The interaction between eyes and session was not significant ($F(1.936, 23.231) = 0.514$, $p = .599$, $\eta_p^2 = .041$).

The main effect of drug was not significant ($F(1, 12) = 3.930$, $p = .071$, $\eta_p^2 = .247$). The means (*SE*) for the modafinil and placebo conditions were 2.288 (0.661) and 3.068 (1.020), respectively.

The main effect of eyes was not significant ($F(1, 12) = .352$, $p = .564$, $\eta_p^2 = .029$). The means (*SE*) for the eyes closed and eyes open conditions were 2.918 (1.009) and 2.438 (0.842), respectively.

The assumption of sphericity was violated for the main effect of session ($\chi^2(9) = 37.639$, $p < .001$, $\varepsilon = .414$). The main effect of session was significant ($F(1.658, 19.895) = 4.034$, $p = .040$, $\eta_p^2 = .252$). Post-hoc analyses indicated that the baseline session had significantly lower percent power than sessions 2 and 4. Session 1 also had significantly less percent power than sessions 2 through 4. This effect is illustrated in Figure 52.

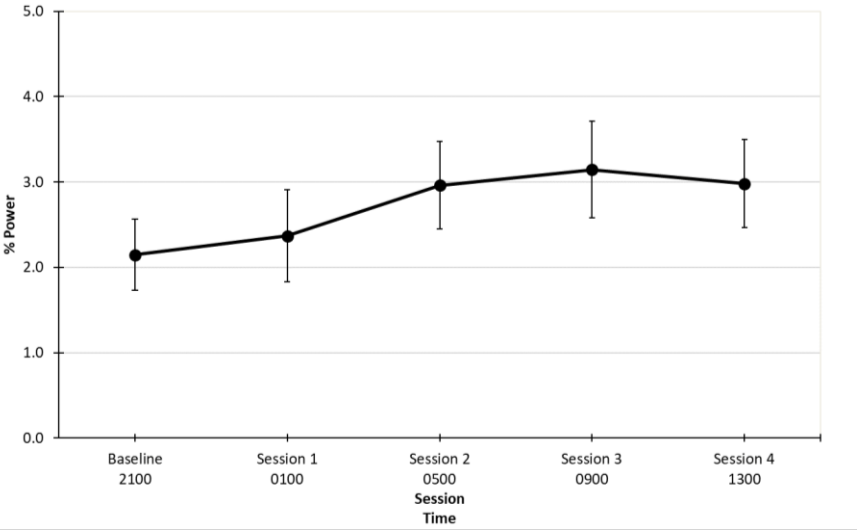


Figure 52. Pz Delta Percent Power: Session Main Effect ($M \pm SE$)

PZ-Alpha: The assumption of sphericity was violated for the three-way interaction among drug, session, and eyes ($\chi^2(9) = 40.262$, $p < .001$, $\varepsilon = .391$). The three-way interaction among drug, session, and eyes was not significant ($F(8.996, 52.738) = 2.047$, $p = .164$, $\eta_p^2 = .146$).

The assumption of sphericity was violated for the interaction between drug and session ($\chi^2(9) = 47.977$, $p < .001$, $\varepsilon = .444$). There was no significant drug by session interaction ($F(7.735,$

21.299) = 0.755, p = .467, η_p^2 = .059), nor a drug by eyes interaction (F(1, 12) = 1.263, p = .283, η_p^2 = .095).

The assumption of sphericity was violated for the interaction between session and eyes (χ^2(9) = 33.079, p < .001, ε = .676). The interaction between session and eyes was not significant (F(2.703, 32.436) = 1.408, p = .259, η_p^2 = .105).

The main effect of drug was not significant (F(1, 12) = 0.055, p = .819, η_p^2 = .005). The means (*SE*) for the modafinil and placebo conditions were 3.059 (1.023) and 3.026 (1.020), respectively.

The assumption of sphericity was violated for the main effect of session (χ^2(9) = 36.074, p < .001, ε = .508). The main effect of session was not significant (F(2.031, 24.375) = 2.218, p = .130, η_p^2 = .156).

The main effect of eyes was not significant (F(1, 12) = 0.060, p = .810, η_p^2 = .005). The means (*SE*) for the eyes closed and eyes open conditions were 3.013 (1.014) and 3.072 (1.038), respectively.

PZ-Beta: There was no significant drug by session by eyes interaction (F(4, 48) = 1.039, p = .397, η_p^2 = .080), nor a drug by eyes interaction (F(1, 12) = .009, p = .924, η_p^2 = .001).

The assumption of sphericity was violated for the interaction between drug and session (χ^2(9) = 21.163, p = .013, ε = .638). The interaction between drug and session was not significant (F(2.550, 30.604) = 0.402, p = .721, η_p^2 = .032).

The assumption of sphericity was violated for the interaction between session and eyes (χ^2(9) = 25.485, p = .003, ε = .617). The interaction between session and eyes was not significant (F(2.468, 29.621) = .834, p = .466, η_p^2 = .065).

The main effect of drug was not significant (F(1, 12) = 0.429, p = .525, η_p^2 = .035), nor was the main effect for session (F(4,48) = 1.774, p = .149, η_p^2 = .129). The means (*SE*) for the modafinil and placebo conditions were 0.264 (0.051) and 0.272 (0.054), respectively.

The main effect of eyes was significant (F(1, 12) = 7.179, p = .020, η_p^2 = .374). There was significantly greater percent power during the eyes-open condition than during the eyes-closed condition. The means (*SE*) for the eyes-open and eyes-closed conditions were 0.296 (0.062) and 0.239 (0.044), respectively.

3.2.1.9 Auditory event-related potentials (ERP) were recorded using a variation of the P300 oddball task. The ERPs for the oddball task included frequency-domain assessment of alpha power near the P3b peak. Time-domain analyses will be presented in a separate report. Time-varying power was computed for the continuous Pz signal in each trial using a family of complex Morlet wavelets (50 wavelets at linearly spaced frequencies from 1-20 Hz, cycle number increasing linearly from 3-20 cycles) with custom MATLAB (2016a, The Mathworks, Inc., Natick, MA) routines based on Cohen (2014). Z-scored power was computed for each frequency

relative to trial power in that frequency. Signal spectra were epoched from stimulus presentation -100 ms to +2000 ms. Average spectra were calculated for oddball and neutral responses for each trial. Mean z-scored slow-alpha (8-10 Hz) activity from 500-800ms post-stimulus was used to compute oddball-neutral power for statistical tests. Data were missing in a session from one participant (placebo, session 1), so the mean replacement was performed for this session. Thus, no participants were excluded, and the total sample size remained at 22. Data were analyzed with a two-way ANOVA, with factors of drug (modafinil and placebo) and session (BL and sessions 1 through 4).

There was no drug by session interaction ($F(4,84) = 1.9378$, $p = 0.112$, $\eta_p^2 = 0.084$), nor a main effect of drug ($F(1,21) = 0.062$, $p = 0.806$, $\eta_p^2 = 0.003$). The means (*SE*) for the placebo and modafinil conditions were -96.272 (30.829) a.u. and -91.726 (29.735), respectively.

The assumption of sphericity was violated for the main effect of session ($\chi^2(9) = 24.008$, $p = 0.004$, $\varepsilon = 0.730$). There was no main effect of session ($F(2.919, 61.292) = 2.588$, $p = 0.063$, $\eta_p^2 = 0.110$).

3.1.1.10 Vital sign measurements.

The metrics analyzed for the vital sign assessments included diastolic and systolic blood pressure, heart rate, and temperature.

Diastolic pressure: The repeated measures ANOVA did not show a significant interaction between drug and session ($F(4, 84) = 0.351$, $p = .842$, $\eta_p^2 = .016$). The pattern of response is illustrated in Figure 53.

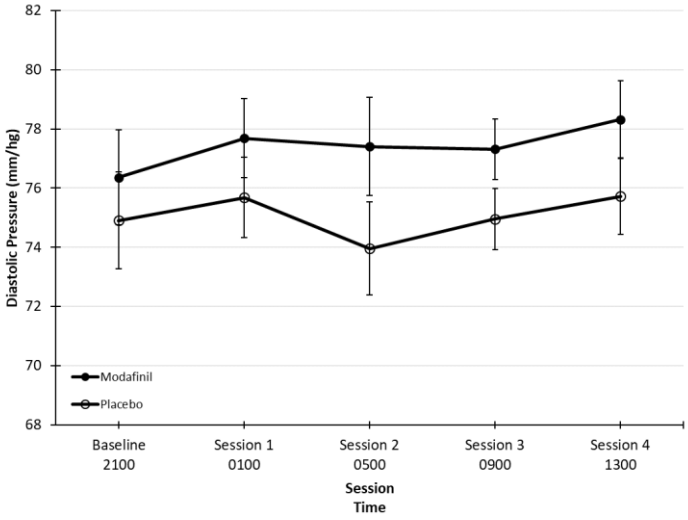


Figure 53. Diastolic Pressure: Drug by Session Interaction ($M \pm SE$)

There was a significant main effect for drug ($F(1, 21) = 9.358$, $p = .006$, $\eta_p^2 = .308$) with significantly higher pressure during the modafinil condition than during the placebo condition.

The means (*SE*) for the modafinil and placebo conditions were 77.418 (1.147) and 75.045 (1.136), respectively.

There was not a significant main effect for session ($F(4, 84) = 0.852$, $p = .497$, $\eta_p^2 = .039$). Diastolic pressure tended to remain steady throughout the data collection period.

Systolic pressure: The repeated measures ANOVA did not show a significant interaction between drug and session ($F(4, 84) = 1.515$, $p = .205$, $\eta_p^2 = .067$). There also was not a significant main effect for drug ($F(1, 21) = 3.366$, $p = .081$, $\eta_p^2 = .138$). The means (*SE*) for modafinil and placebo conditions were 123.291 (1.637) and 121.264 (1.466), respectively. The pattern of responses is shown in Figure 54.

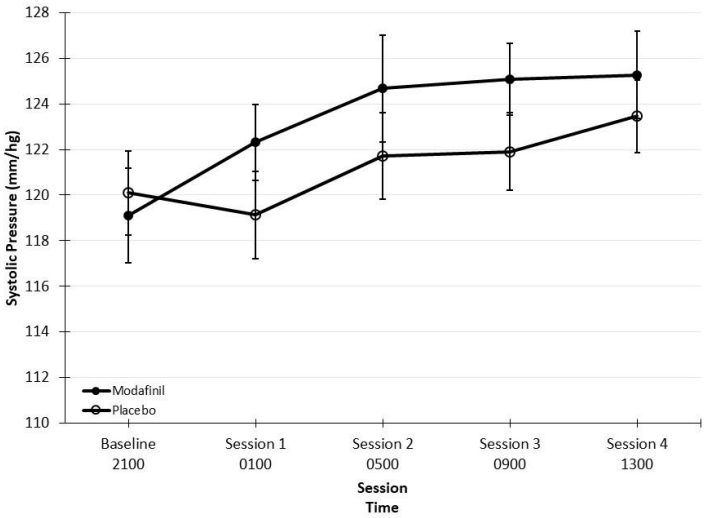


Figure 54. Systolic Pressure: Drug by Session Interaction ($M \pm SE$)

There was a significant main effect for session ($F(4, 84) = 5.154$, $p = .001$, $\eta_p^2 = .197$). Post hoc comparisons showed significantly lower pressure at the baseline session than at sessions 2 through 4, and significantly lower pressure at session 1 compared to sessions 2 through 4. The effects are shown in Figure 55.

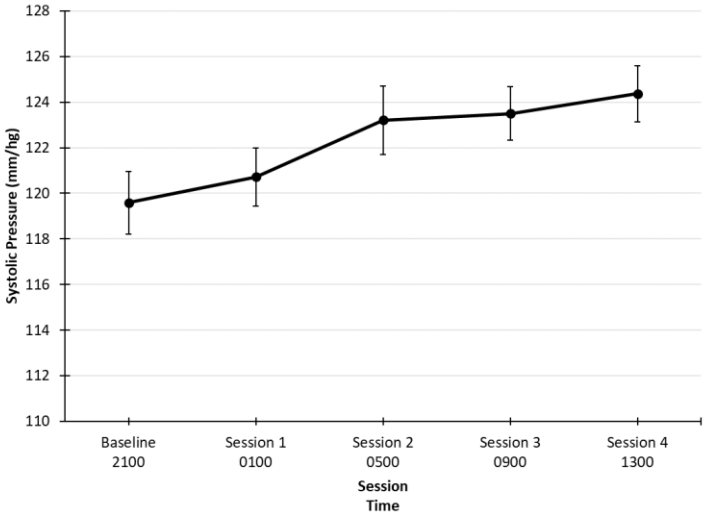


Figure 55. Systolic Pressure: Session Main Effect ($M \pm SE$)

Heart rate: The repeated measures ANOVA did not show a significant interaction between drug and session ($F(4, 84) = 0.537$, $p = .709$, $\eta_p^2 = .025$). The pattern of responses is shown in Figure 56.

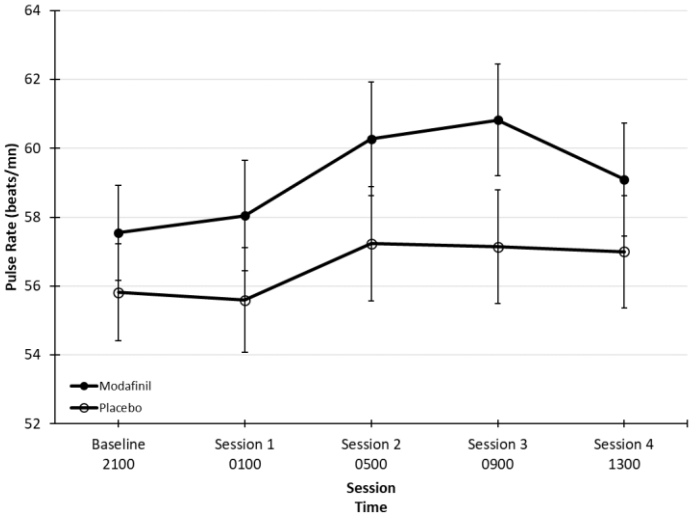


Figure 56. Heart Rate: Drug by Session Interaction ($M \pm SE$)

There was a significant main effect for drug ($F(1, 21) = 8.253$, $p = .009$, $\eta_p^2 = .282$), with heart rate higher during the modafinil condition than during the placebo condition. The means (*SE*) for the modafinil and placebo conditions were 59.155 (1.403) and 56.555 (1.376), respectively.

There also was a significant main effect for session ($F(4, 84) = 2.691$, $p = .036$, $\eta_p^2 = .114$). Post hoc comparisons indicated heart rates were significantly slower at the baseline session than at session 3; session 1 was significantly slower than sessions 2 and 3. The effect is shown in Figure 57.

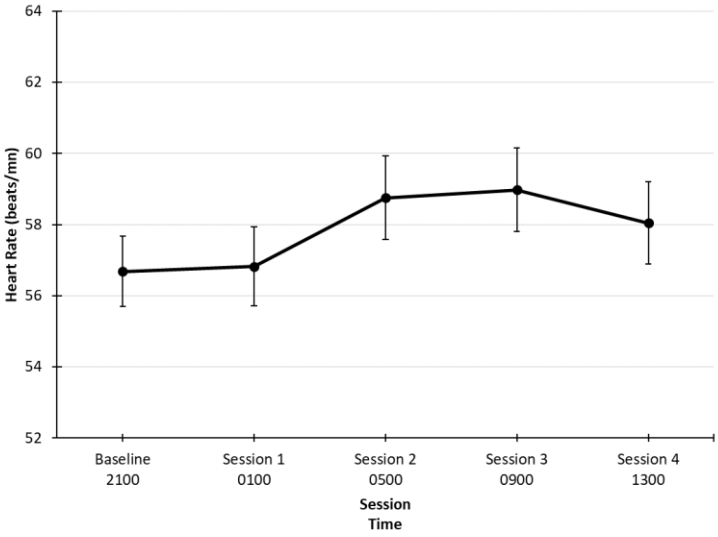


Figure 57. Heart Rate: Session Main Effect ($M \pm SE$)

Temperature: The repeated measures ANOVA did not show a significant interaction between drug and session ($F(4, 84) = 0.703$, $p = .592$, $\eta_p^2 = .032$). There also was not a significant main effect for drug ($F(1, 21) = 0.844$, $p = .369$, $\eta_p^2 = .039$). The effect is illustrated in Figure 58.

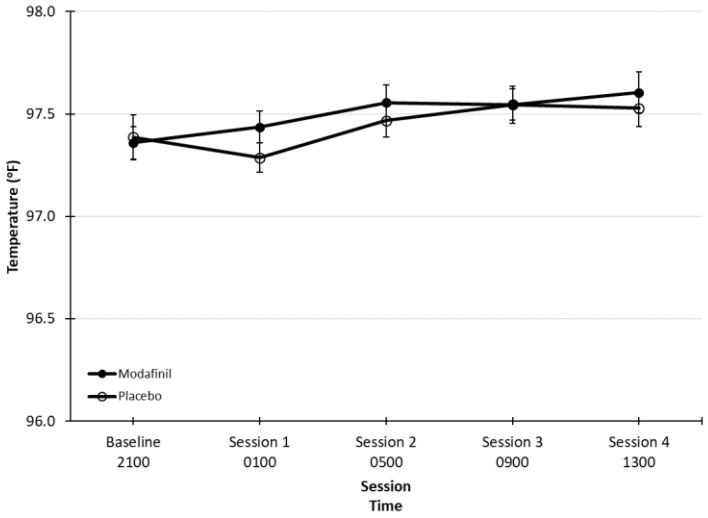


Figure 58. Temperature: Drug by Session Interaction ($M \pm SE$)

The assumption of sphericity was violated for the session main effect ($\chi^2(9) = 18.275$, $p = .033$, $\varepsilon = .776$). There was a significant main effect for session ($F(3.103, 65.172) = 3.694$, $p = .015$, $\eta_p^2 = .150$). Post hoc comparisons indicated temperature was significantly lower at session 1 than sessions 2 through 4. The effect is shown in Figure 59

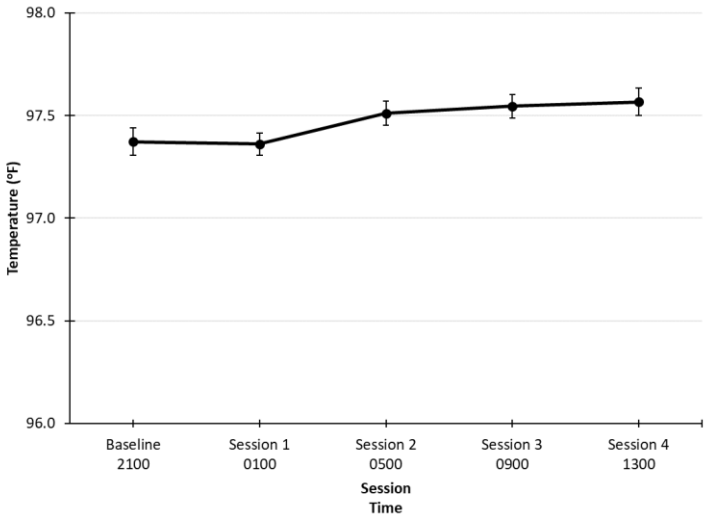


Figure 59. Temperature: Session Main Effect (*M* ± *SE*)

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

3.1.2.1 POMS. All six factors from the *POMS* – tension, depression, anger, vigor, fatigue, confusion, and the Total Mood Disturbance score – were analyzed. One person had missing data due to technical issues with the questionnaire program. Therefore, 21 participants are included in this data analysis.

Tension: There was not a significant interaction between drug and session ($F(4, 80) = 0.817$, $p = .518$, $\eta_p^2 = .039$), a significant main effect of drug ($F(1, 20) = 0.225$, $p = .640$, $\eta_p^2 = .011$), nor a significant main effect of session ($F(4, 80) = 1.217$, $p = .310$, $\eta_p^2 = .057$). The pattern of responses is shown in Figure 60.

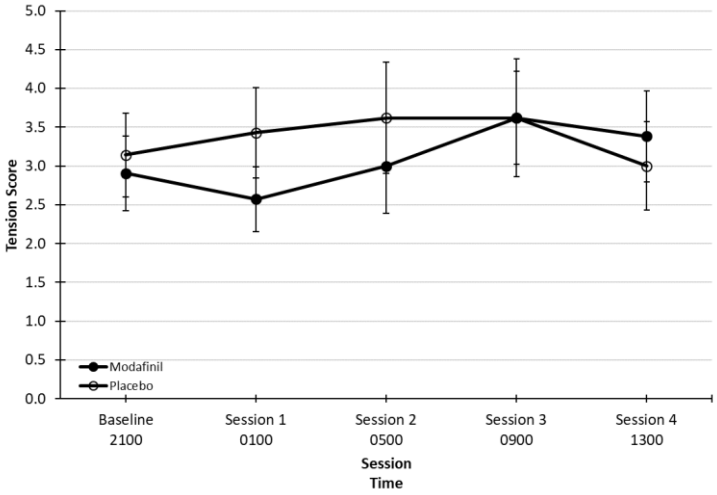


Figure 60. POMS Tension Factor: Drug by Session Interaction (*M* ± *SE*)

Depression: Mauchly's Test of Sphericity was violated for the drug by session interaction ($\chi^2(9) = 61.840$, $p < .001$, $\varepsilon = .410$) and for the main effect for session ($\chi^2(9) = 49.310$, $p < .001$, $\varepsilon = .529$). There was not a significant interaction between drug and session ($F(1.640, 32.807) = 0.579$, $p = .533$, $\eta_p^2 = .028$), a significant main effect of drug ($F(1, 20) = 2.832$, $p = .108$, $\eta_p^2 = .124$) nor a significant main effect of session ($F(2.116, 42.313) = 2.209$, $p = .120$, $\eta_p^2 = .099$). The pattern of responses is shown in Figure 61.

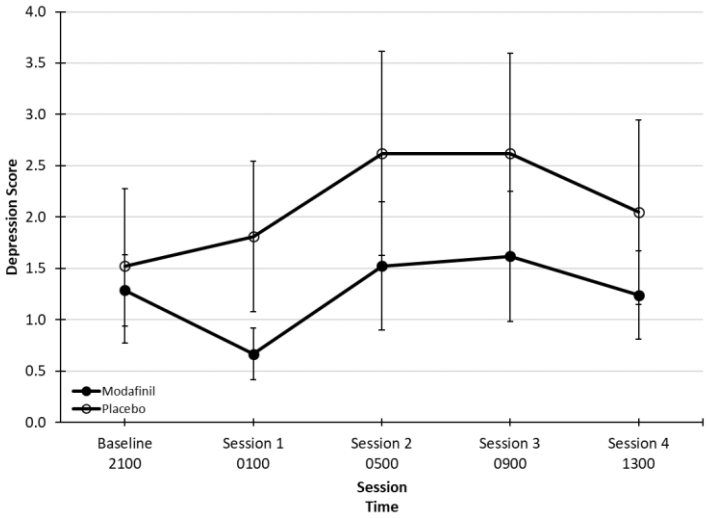


Figure 61. POMS Depression Factor: Drug by Session Interaction ($M \pm SE$)

Anger: Mauchly's Test of Sphericity was violated for the drug by session interaction ($\chi^2(9) = 39.842$, $p < .001$, $\varepsilon = .681$) and for the main effect of session ($\chi^2(9) = 17.164$, $p = .047$, $\varepsilon = .787$). There was a significant interaction between drug and session ($F(2.722, 54.449) = 3.519$, $p = .024$, $\eta_p^2 = .150$). Post-hoc analyses revealed significantly lower ratings of anger at session 1 in the modafinil condition compared to the placebo condition. Within the modafinil condition, ratings of anger were significantly lower in session 1 compared to session 3. None of the sessions were significantly different within the placebo condition. These effects are shown in Figure 62.

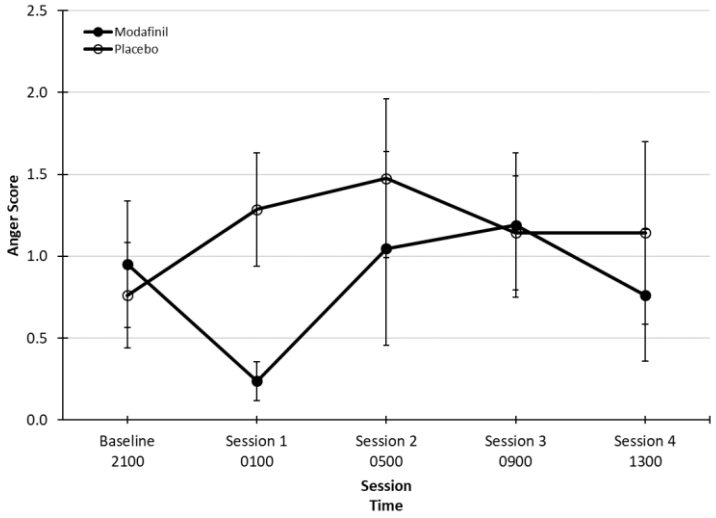


Figure 62. POMS Anger Factor: Drug by Session Interaction ($M \pm SE$)

There was not a significant main effect for drug ($F(1, 20) = 1.850$, $p = .189$, $\eta_p^2 = .085$) nor a significant main effect of session ($F(3.146, 62.926) = 0.817$, $p = .494$, $\eta_p^2 = .039$).

Vigor: There was a significant two-way interaction between drug and session ($F(4,80) = 9.122$, $p < .001$, $\eta_p^2 = .313$). Post-hoc comparisons revealed significantly higher vigor ratings during the modafinil condition at sessions 1 and 2 compared to the placebo condition. Within the modafinil condition, the baseline session and session 1 ratings of vigor were significantly greater than sessions 2 through 4. Within the placebo condition, the baseline session ratings of vigor were significantly greater than sessions 1 through 3; session 1 ratings were significantly greater than session 2; and session 2 ratings were significantly lower than sessions 3 and 4. These effects are illustrated in Figure 63.

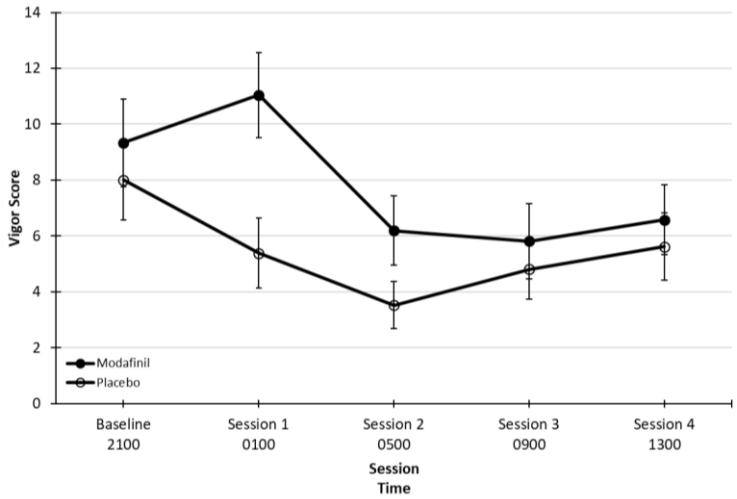


Figure 63. POMS Vigor Factor: Drug by Session Interaction ($M \pm SE$)

There was a significant main effect for drug ($F(1,20) = 15.108$, $p = .001$, $\eta_p^2 = .430$) such that ratings of vigor were greater during the modafinil condition compared to placebo. The means (*SE*) for the modafinil and placebo conditions were 7.790 (1.252) and 5.467 (1.063), respectively.

Mauchly's Test of Sphericity was violated for the main effect of session ($\chi^2(9) = 19.439$, $p = .022$, $\varepsilon = .755$). There was a significant main effect for session ($F(3.021, 60.419) = 10.361$, $p < .001$, $\eta_p^2 = .341$). Post-hoc comparisons revealed significantly greater vigor ratings at the baseline session and session 1 compared to sessions 2 through 4, and lower ratings of vigor at session 2 compared to session 4. This is illustrated in Figure 64.

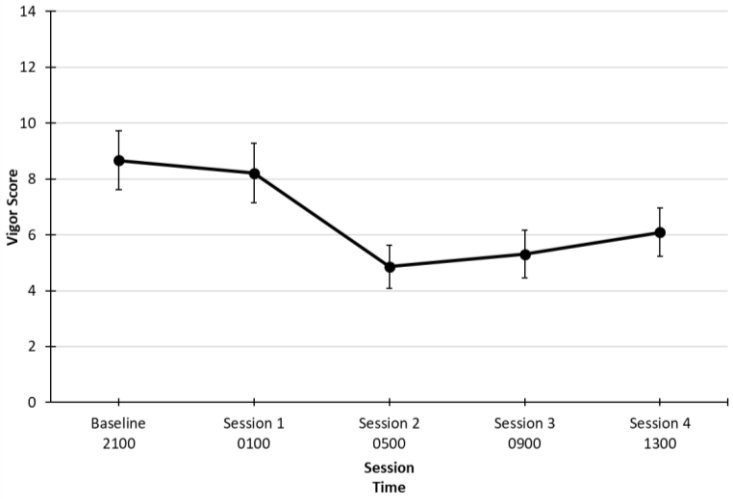


Figure 64. POMS Vigor Factor: Session Main Effect ($M \pm SE$)

Fatigue: Mauchly's Test of Sphericity was violated for the drug by session interaction ($\chi^2(9) = 21.896$, $p = .009$, $\varepsilon = .720$). There was a significant two-way interaction between drug and session ($F(2.880, 57.594) = 3.110$, $p = .035$, $\eta_p^2 = .135$). Post-hoc comparisons revealed significantly lower fatigue scores during the modafinil condition compared to the placebo condition at sessions 1 through 3, with the difference between the two conditions at the baseline session approaching statistical significance ($p = .052$). Within the modafinil condition, the baseline session and session 1 ratings of fatigue were significantly lower than sessions 2 through 4. Within the placebo condition, the baseline session ratings of fatigue were significantly lower than sessions 1 through 4; session 1 ratings were significantly lower than sessions 2 and 3. The effects are shown in Figure 65.

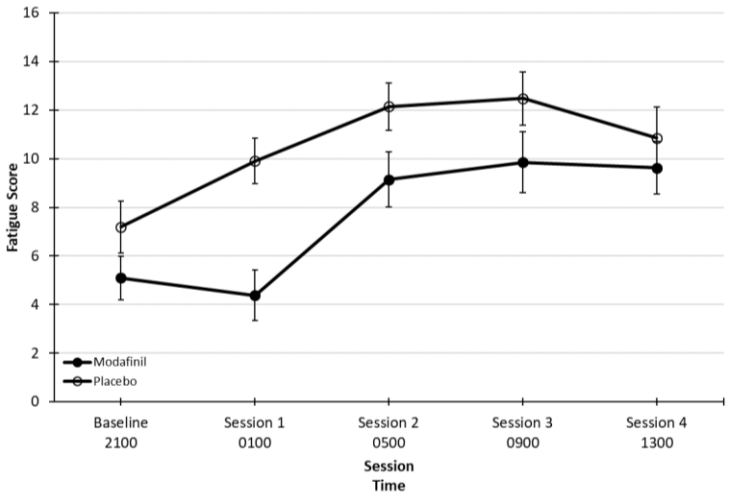


Figure 65. POMS Fatigue Factor: Drug by Session Interaction (*M* ± *SE*)

There was a significant main effect for drug ($F(1,20) = 11.850$, $p = .003$, $\eta_p^2 = .372$). Fatigue ratings were lower during the modafinil condition than during the placebo condition. The means (*SE*) for the modafinil and placebo conditions were 7.619 (0.928) and 10.514 (0.867), respectively.

Mauchly's Test of Sphericity was violated for the main effect of session ($\chi^2(9) = 18.310$, $p = .009$, $\varepsilon = .833$). There was a significant main effect for session ($F(3.334, 66.673) = 19.824$, $p < .001$, $\eta_p^2 = .498$). Pairwise comparisons indicated the fatigue ratings during the baseline session and session 1 were significantly lower than the ratings during sessions 2 through 4. These effects are shown in Figure 66.

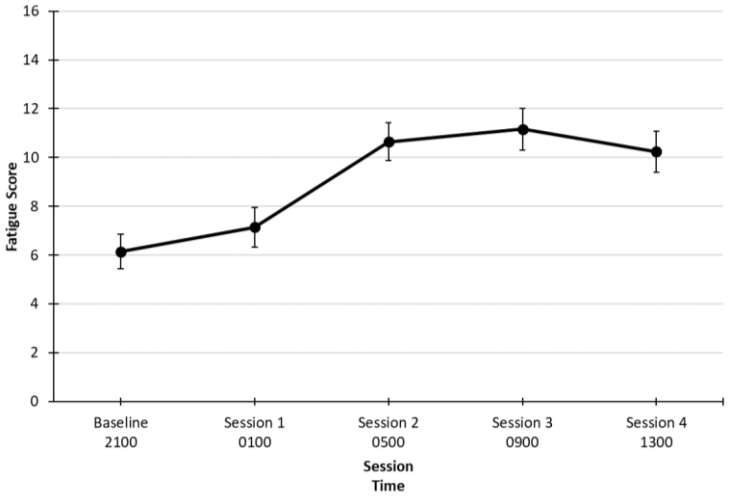


Figure 66. POMS Fatigue Factor: Session Main Effect (*M* ± *SE*)

Confusion: The repeated measures ANOVA did not show a significant interaction between drug and session ($F(4, 80) = 1.444$, $p = .227$, $\eta_p^2 = .067$). The main effect for drug approached

statistical significance ($F(1, 20) = 4.282$, $p = .052$, $\eta_p^2 = .176$). The means (*SE*) for the modafinil and placebo conditions were 2.933 (0.375) and 3.648 (0.422), respectively. The pattern of responses between drug and session is illustrated in Figure 67.

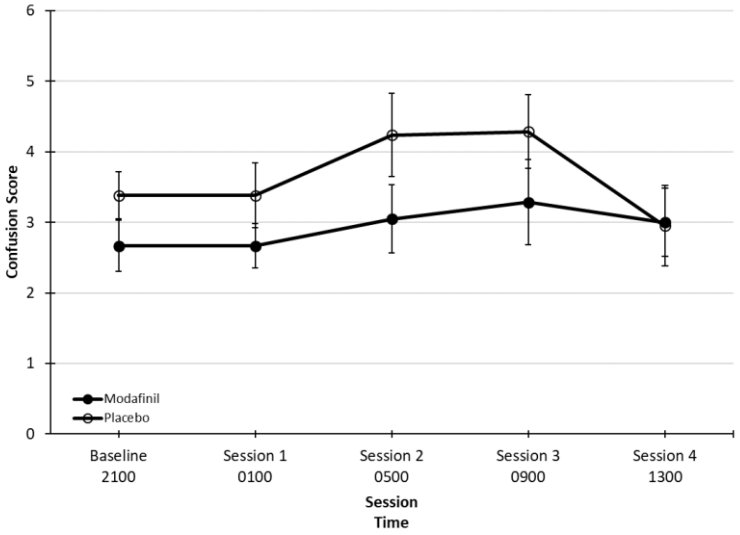


Figure 67. POMS Confusion Factor: Drug by Session Interaction ($M \pm SE$)

There was a significant main effect for session ($F(4, 80) = 2.815$, $p = .031$, $\eta_p^2 = .123$). Post hoc analyses indicated significantly lower scores of confusion at the baseline session and session 1 compared to session 3, and significantly higher scores at session 3 compared to session 4. The effect is illustrated in Figure 68.

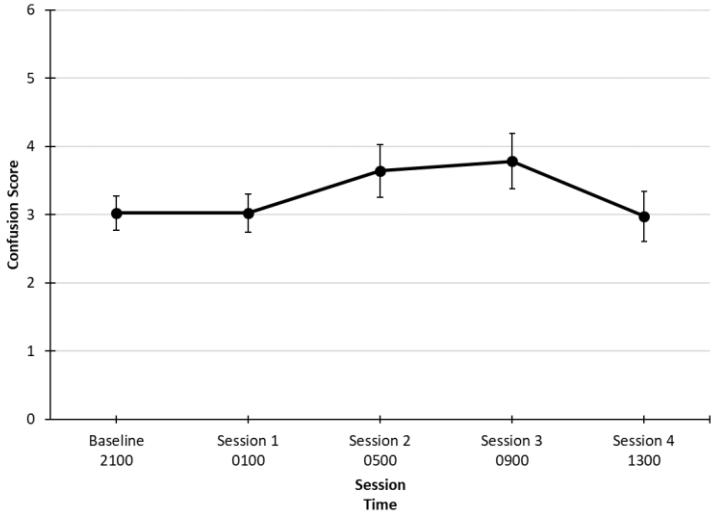


Figure 68. POMS Confusion Factor: Session Main Effect ($M \pm SE$)

Total Mood Disturbance (TMD): Mauchly's Test of Sphericity was violated for the drug by session interaction ($\chi^2(9) = 28.506$, $p = .001$, $\varepsilon = .593$). There was a significant interaction between drug and session ($F(2.374, 47.474) = 5.036$, $p = .007$, $\eta_p^2 = .201$). The post hoc analyses

indicated lower total mood scores during the modafinil condition at sessions 1 through 3 compared to the placebo condition. Within the modafinil condition, the baseline session and session 1 were significantly lower than sessions 2 through 4; session 2 scores were significantly lower than session 3. Within the placebo condition, scores at the baseline session were significantly lower than sessions 1 through 3 (marginally at session 4, $p = .054$); session 1 scores were significantly lower than those at sessions 2 and 3; and session 3 scores were significantly higher than those at session 4. This pattern of responses is illustrated in Figure 69.

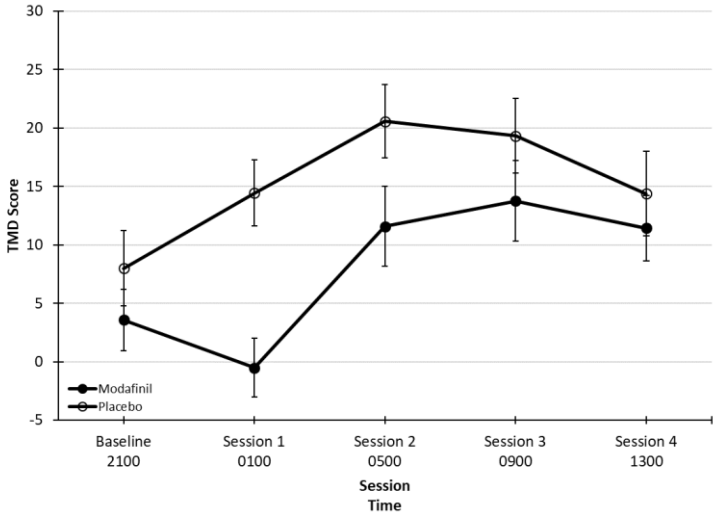


Figure 69. POMS TMD Score: Drug by Session Interaction ($M \pm SE$)

There was a significant main effect for drug ($F(1, 20) = 12.499$, $p = .002$, $\eta_p^2 = .385$) such that scores were significantly lower during the modafinil condition than during the placebo condition. The means (*SE*) for the modafinil and placebo conditions were 7.962 (2.515) and 15.343 (2.904), respectively.

Mauchly's Test of Sphericity was violated for the main effect of session ($\chi^2(9) = 21.448$, $p = .011$, $\varepsilon = .729$). There was a significant main effect for session ($F(2.918, 58.358) = 15.039$, $p < .001$, $\eta_p^2 = .429$). Post hoc analyses indicated significantly lower scores at the baseline session and session 1 compared to sessions 2 through 4; session 3 was significantly higher than session 4. These effects are shown in Figure 70.

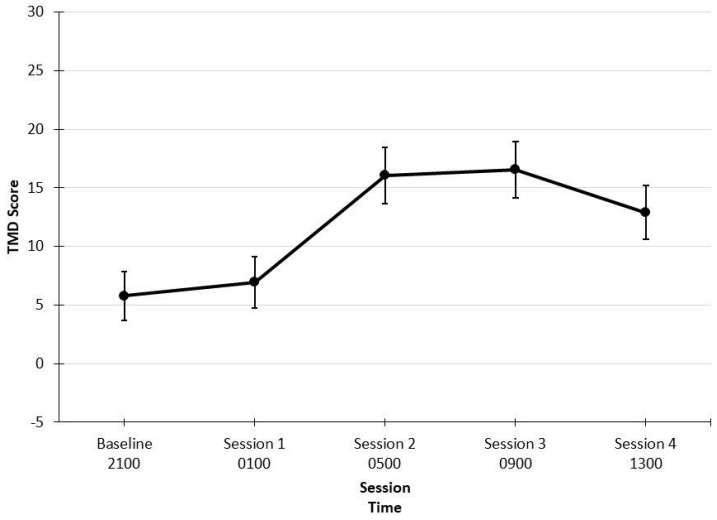


Figure 70. POMS TMD Score: Session Main Effect (*M* ± *SE*)

3.1.2.2 VAS. All eight factors from the *VAS* – alert/able to concentrate, anxious, energetic, confident, irritable, jittery/nervous, sleepiness, and talkative – were analyzed, and the results from these analyses are presented below.

Alert/able to concentrate: There was a significant interaction between drug and session ($F(4, 84) = 5.700$, $p < .001$, $\eta_p^2 = .213$). Post hoc analyses showed significant differences between the drug conditions at sessions 1 through 3, with higher scores during the modafinil condition than during the placebo condition. Within the modafinil condition, the baseline session and session 1 ratings of alertness/ability to concentrate were significantly higher than sessions 2 through 4. Within the placebo condition, the baseline session ratings were significantly higher than sessions 2 through 4; session 1 was significantly higher than sessions 2 and 3. These results are illustrated in Figure 71.

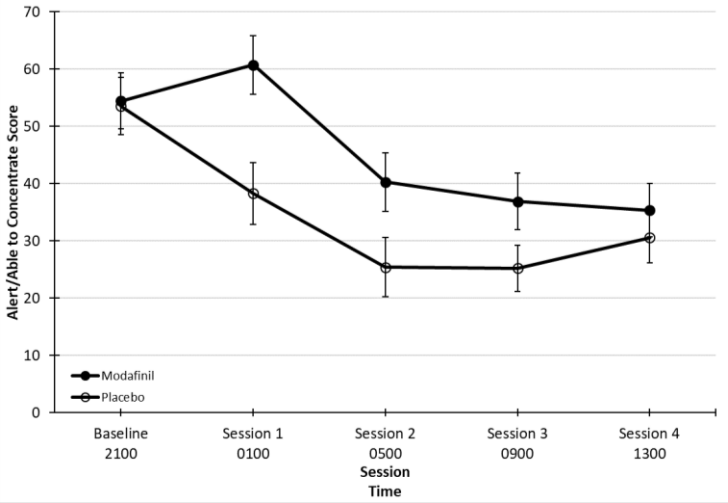


Figure 71. VAS Alert/Able to Concentrate Score: Drug by Session Interaction (*M* ± *SE*)

There was a significant main effect for drug ($F(1, 21) = 10.803$, $p = .004$, $\eta_p^2 = .340$), with the modafinil condition showing higher ratings than the placebo condition. The means (*SE*) for the modafinil and placebo conditions were 45.536 (4.270) and 34.618 (3.752), respectively.

The assumption of sphericity for the session main effect was violated ($\chi^2(9) = 18.593$, $p = .029$, $\varepsilon = .810$). There was a significant main effect for session ($F(3.241, 68.058) = 17.749$, $p < .001$, $\eta_p^2 = .458$). Post hoc analyses revealed the baseline session and session 1 had significantly higher ratings than sessions 2 through 4. This effect is shown in Figure 72.

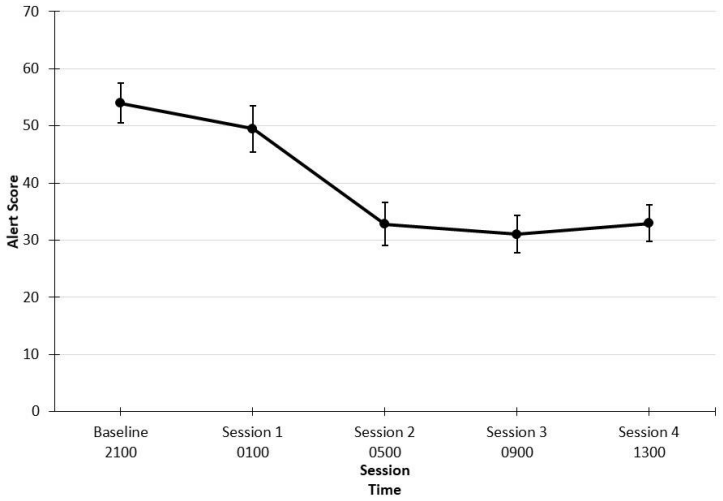


Figure 72. VAS Alert/Able to Concentrate Score: Session Main Effect ($M \pm SE$)

Anxious: There was not a significant interaction between drug and session ($F(4, 84) = 1.837$, $p = .129$, $\eta_p^2 = .080$). There also was not a significant main effect for drug ($F(1, 21) = 0.545$, $p = .469$, $\eta_p^2 = .025$). The pattern of responses is illustrated in Figure 73.

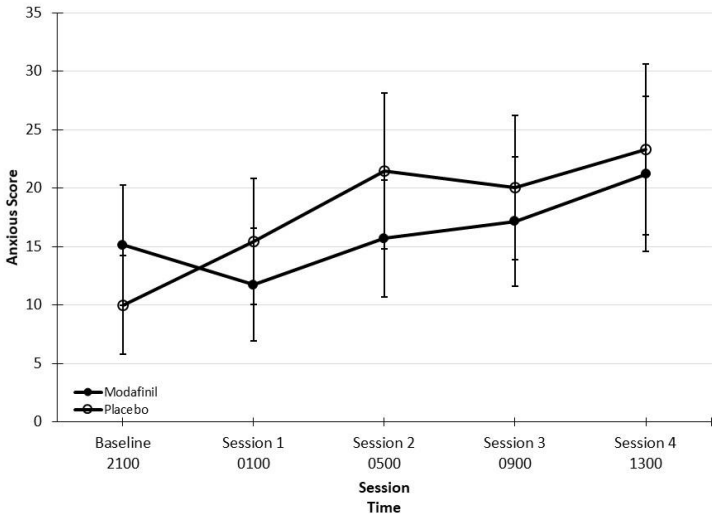


Figure 73. VAS Anxious Score: Drug by Session Interaction ($M \pm SE$)

The assumption of sphericity for the session main effect was violated ($\chi^2(9) = 63.961$, $p < .001$, $\varepsilon = .449$). There was a significant main effect for session ($F(1.796, 37.712) = 3.774$, $p = .036$, $\eta_p^2 = .152$). Post hoc analyses revealed the baseline session had significantly lower ratings of anxiety than sessions 2 through 4; session 1 had significantly lower ratings than sessions 2 and 4. This pattern is shown in Figure 74.

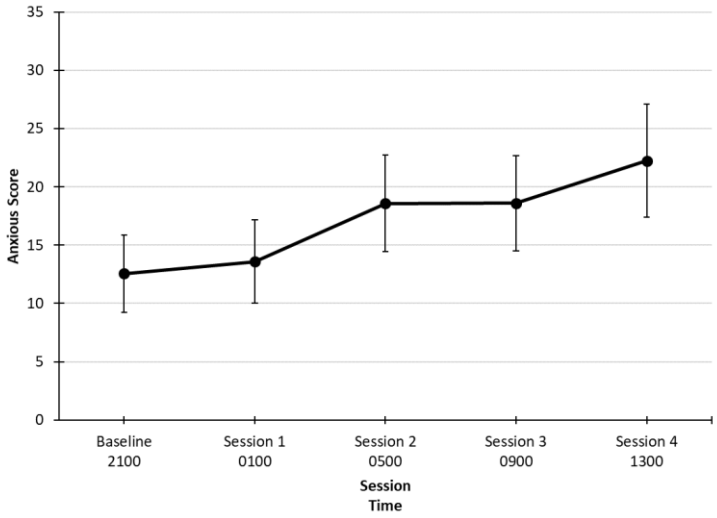


Figure 74. VAS Anxious Score: Session Main Effect ($M \pm SE$)

Energetic: The repeated measures ANOVA revealed a significant interaction between drug and session ($F(4, 84) = 4.338$, $p = .003$, $\eta_p^2 = .171$). Post hoc analyses showed significant differences between the drug conditions at sessions 1 and 2 with higher ratings during the modafinil condition than during the placebo condition. Within the modafinil condition, the baseline session and session 1 ratings were significantly higher than sessions 2 through 4. Within the placebo condition, the baseline session rating was significantly higher than all other sessions; session 1 was significantly higher than session 2. These results are illustrated in Figure 75.

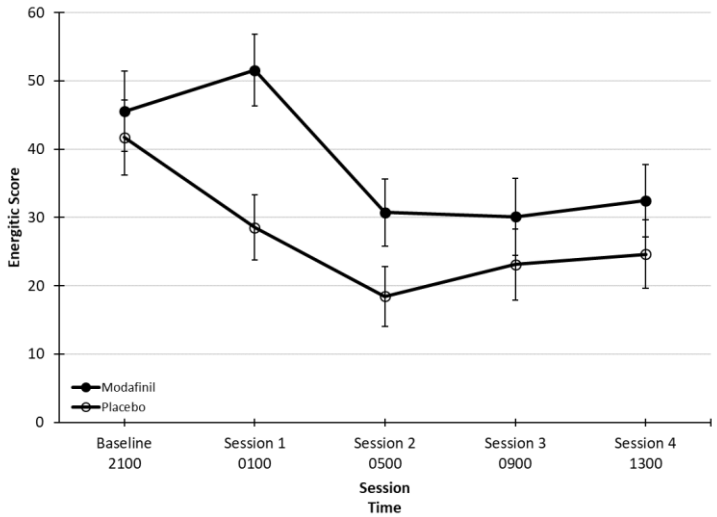


Figure 75. VAS Energetic Score: Drug by Session Interaction ($M \pm SE$)

There was a significant main effect for drug ($F(1, 21) = 15.619$, $p = .001$, $\eta_p^2 = .427$), with the modafinil condition showing higher ratings than the placebo condition. The means (*SE*) for the modafinil and placebo conditions were 38.082 (4.663) and 27.300 (4.348), respectively.

The assumption of sphericity for the session main effect was violated ($\chi^2(9) = 22.661$, $p = .007$, $\varepsilon = .806$). There was a significant main effect for session ($F(3.224, 67.697) = 13.951$, $p < .001$, $\eta_p^2 = .399$). Post hoc analyses revealed the baseline session and session 1 ratings were significantly higher than session 2 through 4. This effect is shown in Figure 76.

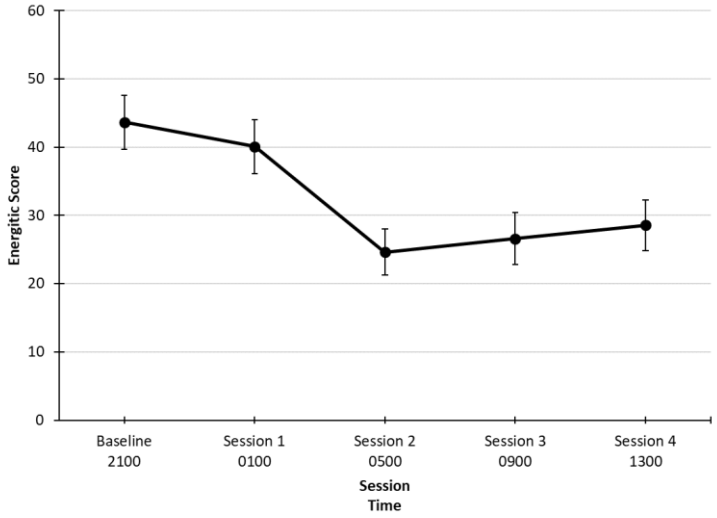


Figure 76. VAS Energetic Score: Session Main Effect (*M* ± *SE*)

Confident: The assumption of sphericity for the drug by session interaction was violated ($\chi^2(9) = 20.613$, $p = .015$, $\varepsilon = .839$). There was not a significant interaction between drug and session ($F(3.354, 70.444) = 1.702$, $p = .169$, $\eta_p^2 = .075$). There was also not a significant main effect for drug ($F(1, 21) = 2.346$, $p = .141$, $\eta_p^2 = .100$). These results are illustrated in Figure 77.

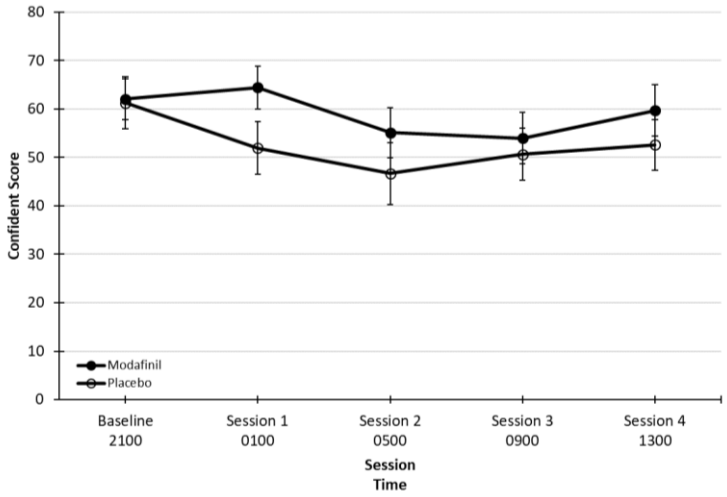


Figure 77. VAS Confident Score: Drug by Session Interaction (*M* ± *SE*)

There was a significant main effect for session ($F(4, 84) = 3.466$, $p = .011$, $\eta_p^2 = .142$). Pairwise comparisons revealed the baseline session rating for confidence was significantly higher than sessions 2 and 3; session 1 was significantly higher than session 2. The effect is illustrated in Figure 78.

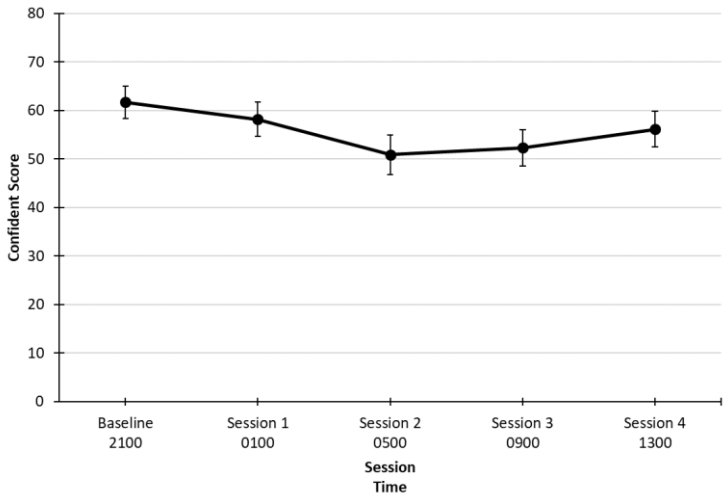


Figure 78. VAS Confident Score: Session Main Effect ($M \pm SE$)

Irritable: The assumption of sphericity for the drug by session interaction was violated ($\chi^2(9) = 21.353$, $p = .011$, $\varepsilon = .888$). There was a significant interaction between drug and session ($F(3.551, 74.567) = 3.090$, $p = .025$, $\eta_p^2 = .128$). Post hoc analyses showed significant differences between the drug conditions at sessions 1 and 2 with ratings of irritability during the modafinil condition lower than during the placebo condition. Within the modafinil condition, the baseline session and session 1 were significantly lower than session 3; session 2 was marginally lower than session 3 ($p = .051$). Within the placebo condition, the baseline session rating was significantly lower than session 2. These results are illustrated in Figure 79.

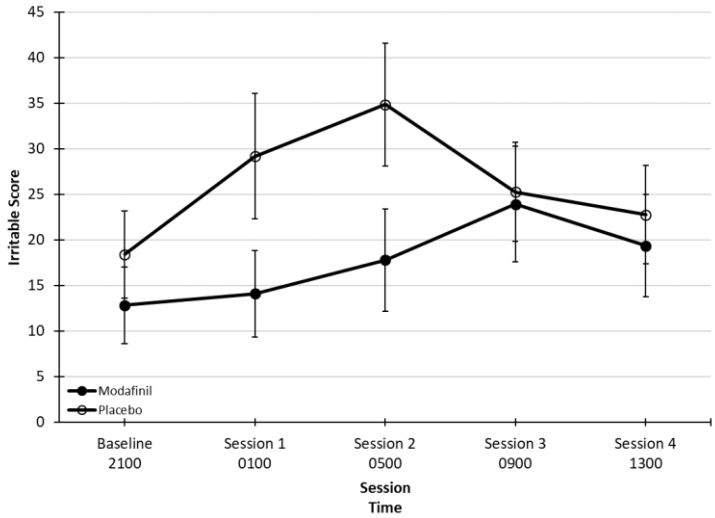


Figure 79. VAS Irritable Score: Drug by Session Interaction ($M \pm SE$)

There was a significant main effect for drug ($F(1, 21) = 7.508$, $p = .012$, $\eta_p^2 = .263$), with the modafinil condition showing lower scores than the placebo condition. The means (*SE*) for the modafinil and placebo conditions were 17.591 (4.868) and 26.100 (4.720), respectively.

The assumption of sphericity for the session main effect was violated ($\chi^2(9) = 17.354$, $p = .044$, $\varepsilon = .876$). There was not a significant main effect for session ($F(3.505, 73.613) = 2.434$, $p = .062$, $\eta_p^2 = .104$).

Jittery: The assumption of sphericity for the drug by session interaction was violated ($\chi^2(9) = 41.120$, $p < .001$, $\varepsilon = .629$). There was not a significant interaction between drug and session ($F(2.516, 52.838) = 1.643$, $p = .197$, $\eta_p^2 = .073$. There was not a significant main effect for drug ($F(1, 21) = 0.548$, $p = .467$, $\eta_p^2 = .025$). These results are illustrated in Figure 80.

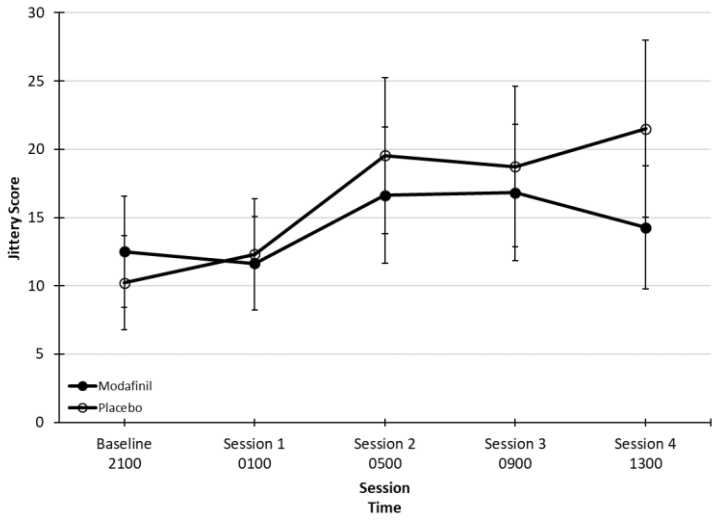


Figure 80. VAS Irritable Score: Drug by Session Interaction ($M \pm SE$)

The assumption of sphericity for the session main effect was violated ($\chi^2(9) = 48.813$, $p < .001$, $\varepsilon = .472$). There was a significant main effect for session ($F(1.889, 39.661) = 3.547$, $p = .041$, $\eta_p^2 = .145$). Pairwise comparisons revealed the baseline session ratings for jittery were significantly lower than session 2, and marginally lower than session 3 ($p = .06$); session 1 ratings were significantly lower than session 2, and marginally lower than session 3 ($p = .055$). The effect is illustrated in Figure 81.

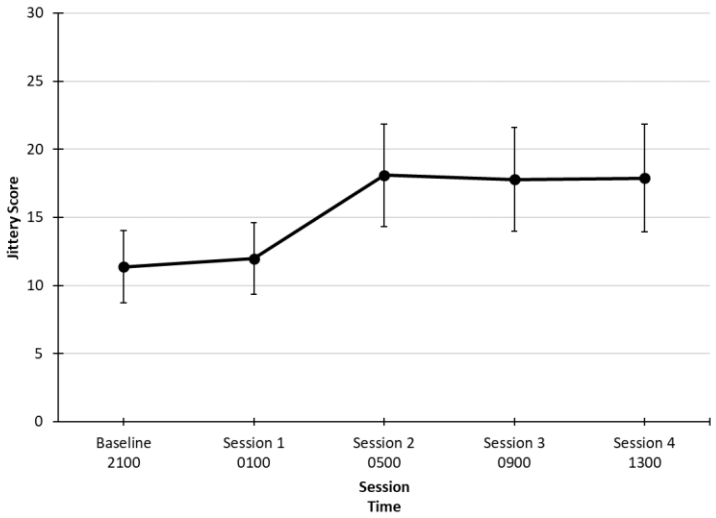


Figure 81. VAS Jittery Score: Session Main Effect ($M \pm SE$)

Sleepiness: The assumption of sphericity for the drug by session interaction was violated ($\chi^2(9) = 26.170$, $p = .002$, $\varepsilon = .713$). There was a significant interaction between drug and session ($F(2.850, 59.858) = 11.031$, $p < .001$, $\eta_p^2 = .344$). Post hoc analyses showed significant differences in ratings of sleepiness between the drug conditions at sessions 1 through 3, with the modafinil condition showing lower ratings than the placebo condition. Within the modafinil condition, the baseline session and session 1 were significantly lower than sessions 2 through 4; session 2 was significantly lower than session 4. Within the placebo condition, the baseline session ratings were significantly lower than sessions 1 through 4; session 1 ratings were lower than sessions 2 and 3. These results are illustrated in Figure 82.

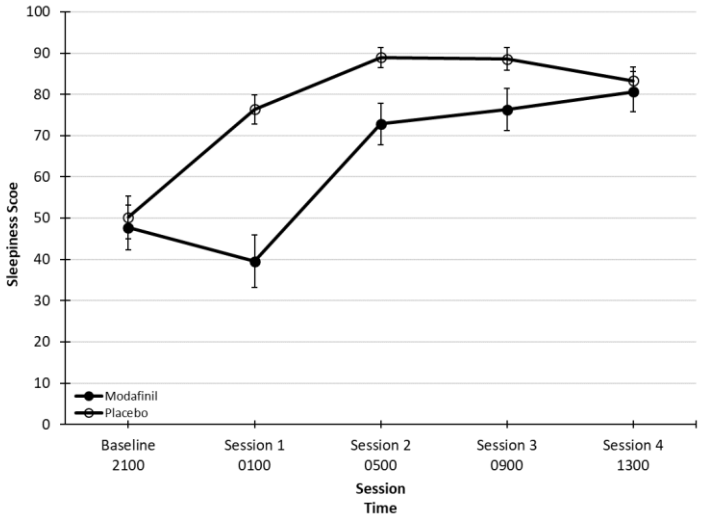


Figure 82. VAS Sleepiness Score: Drug by Session Interaction ($M \pm SE$)

There was a significant main effect for drug ($F(1, 21) = 11.545$, $p = .003$, $\eta_p^2 = .355$), with the modafinil condition showing lower sleepiness ratings than the placebo condition. The means

(*SE*) for the modafinil and placebo conditions were 63.382 (4.126) and 77.455 (2.658), respectively.

The assumption of sphericity for the session main effect was violated ($\chi^2(9) = 37.025$, $p < .001$, $\varepsilon = .641$). There was a significant main effect for session ($F(2.563, 53.826) = 37.850$, $p < .001$, $\eta_p^2 = .643$). Post hoc analyses revealed that the baseline session ratings were significantly lower than all other sessions; session 1 was significantly lower than sessions 2 through 4. This pattern is shown in Figure 83.

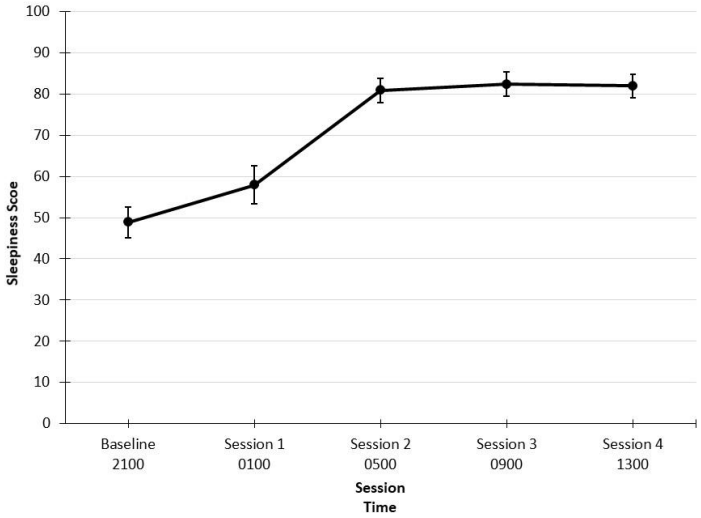


Figure 83. VAS Irritable Score: Session Main Effect (*M* ± *SE*)

Talkative: The assumption of sphericity for the drug by session interaction was violated ($\chi^2(9) = 17.043$, $p = .049$;, $\varepsilon = .858$). There was not a significant interaction between drug and session ($F(3.431, 72.058) = 1.627$, $p = .185$, $\eta_p^2 = .072$). There also was not a significant main effect for drug ($F(1, 21) = 1.083$, $p = .310$, $\eta_p^2 = .049$). These results are illustrated in Figure 84.

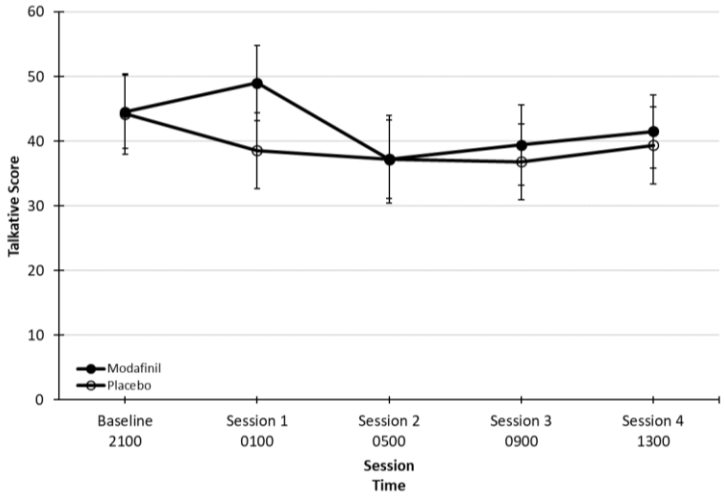


Figure 84. VAS Talkative Score: Drug by Session Interaction (*M* ± *SE*)

There was a significant main effect for session ($F(4, 84) = 4.541$, $p = .002$, $\eta_p^2 = .178$). Post hoc analyses revealed the baseline session and session 1 talkative ratings were significantly higher than sessions 2 and 3. This effect is shown in Figure 85.

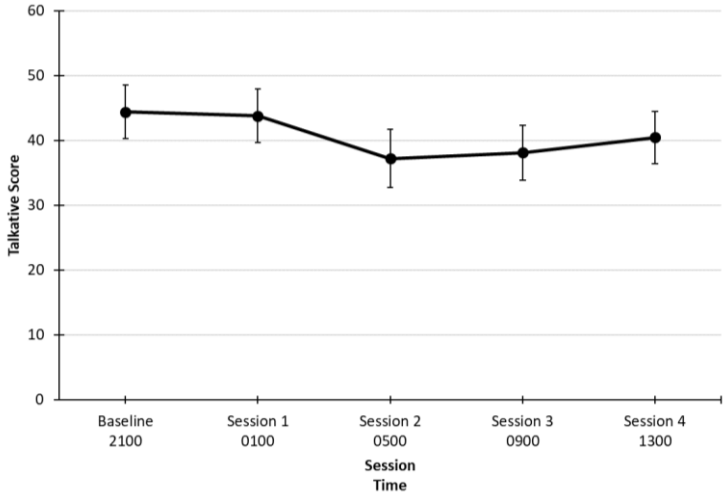


Figure 85. VAS Talkative Score: Drug by Session Interaction ($M \pm SE$)

3.1.2.3 Side effects questionnaire (SEQ). Results examining various side effects were tallied for each factor and are presented in Appendix B. One questionnaire is missing from session 3 of the placebo condition; all other data are included in the tallies. No statistical analyses were performed for responses to side effects. Documentation of these effects were for safety monitoring only.

3.2 Individual differences analyses

The primary analyses to address the hypotheses were conducted in steps to first identify the fatigue-vulnerable and -resistant individuals, followed by the analyses to determine the effects of modafinil on performance based on the fatigue response. To assign individuals into fatigue-vulnerable and -resistant groups, two measures from each test were selected for analysis, one measure of accuracy and one measure of speed if possible. Each test's selected metric from the placebo sessions after midnight (1 through 4) were averaged for each individual. These averaged scores were then ranked from lowest to highest performance on the metrics for each test. The ranked scores were then divided into the top 50 percent and the lowest 50 percent, creating 2 groups, fatigue-vulnerable (lowest scoring) and fatigue-resistant (highest scoring). In some cases, the 50th percentile involved individuals with the same score; rather than putting these individuals in different groups, individuals with the same score were placed in the same group, creating unequal *n*'s in some cases. The choice of group was determined based on the scores immediately preceding and following the 50th percentile score, with group assignment based on the score closest to the middle score. Although none of the participants in the present investigation were completely resistant to the effects of sleep loss, those who performed the best were grouped, per task, as fatigue-resistant, and those who performed the worst were grouped as fatigue-vulnerable.

It was hypothesized that the fatigue-vulnerable group would benefit the most from administration of modafinil.

The average of each participants' amount of sleep obtained from the three nights prior to each participant's placebo run was analyzed by each task metric's grouping to determine if differences in performance between groups were due to differences in the amount of prior sleep obtained. The nights of sleep before the placebo condition were analyzed since the groups were assigned based on performance during the placebo condition.

Once the two groups were identified, the data were analyzed with a three-way mixed-model ANOVA, with fatigue response as the grouping variable (vulnerable and resistant) and drug (modafinil and placebo) and session (the baseline session and sessions 1 through 4) as the repeated factors. Each analysis yielded seven F tests: a main effect of group; a main effect for drug (drug effect); a main effect of time (session effect); 2-way interactions between group and drug, group and session, and drug and session; and a 3-way interaction among group, drug, and time. Mauchly's Test of Sphericity was used to test the assumption of sphericity within sessions. When the sphericity assumption was violated, the Huynh-Feldt correction was used to calculate the F statistic. The results of both the Levine's Test for Equality of Variances and Mauchly's Test of Sphericity are reported only when the assumptions were violated. Significant interactions were followed with analyses of simple effects and Fisher's Least Significant Difference (LSD) tests. Significant main effects for session were further analyzed with LSD tests. All results are presented by task below and summarized in Appendix A.

3.2.1 Cognitive and physiological measures. The series of cognitive evaluations, which were measured during the baseline and continuous wakefulness period following the administration of the drug, were examined for the fatigue response analyses. Each group's *n* is reported for each metric examined. In addition, participant ID numbers are included with the figure illustrating the group by drug by session relationship.

3.2.1.1 Psychomotor Vigilance Test (PVT). Unlike the other tests which were administered once each test session, the PVT was administered every hour starting at 1200 on Day 1 with the last test at 1700 on Day 2. For the analyses identifying fatigue response groups, only the tests from the beginning of each session were used to correspond with the number of sessions from the other tests to facilitate better comparisons. This reduced set of tests for the PVT resulted in a 2 (drug) by 2 (group) by 5 (session) repeated measures ANOVA. The metrics analyzed for this task were the number of lapses (RTs > 500msec) and the reciprocal reaction time (RRT). This data set did not have outliers as did the full data set; therefore, all 22 individuals were included in these analyses.

Lapses: The grouping resulted in 10 individuals in the fatigue-resistant group and 12 in the fatigue-vulnerable group. The average (*SD*) hours of sleep obtained the 3 nights before the placebo visit to the lab were 8.22 (0.38) for the fatigue-resistant group and 8.27 (0.45) for the fatigue-vulnerable group ($t(20) = -0.302$, $p = .765$).

There was not a significant group by drug by session interaction ($F(4, 80) = 1.623$, $p = .176$, $\eta_p^2 = .075$). Figure 86 shows the relationship among group, drug, and session.

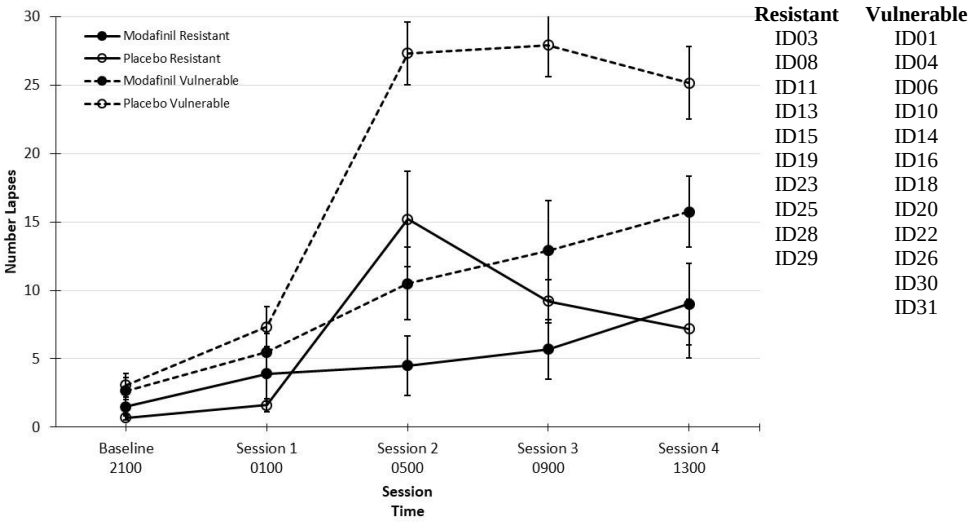


Figure 86. PVT Lapses: Group by Drug by Session Interaction ($M \pm SE$)

There was a significant group by drug interaction ($F(1, 20) = 11.235$, $p = .003$, $\eta_p^2 = .360$). Post hoc analyses indicated a significant difference between the two groups during the placebo condition, but only approaching statistical significance during the modafinil condition ($p = .055$). The fatigue-vulnerable group had better performance during the modafinil condition than during the placebo condition, whereas the fatigue-resistant group's performance did not differ between the two drugs. The effects are illustrated in Figure 87.

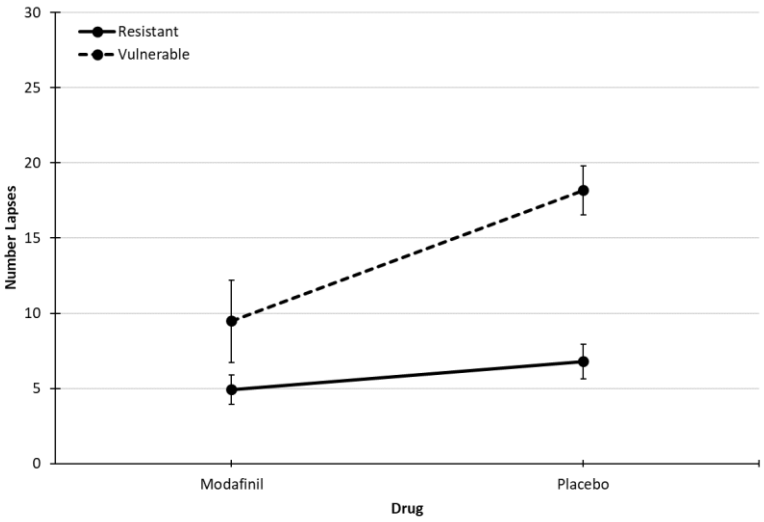


Figure 87. PVT Lapses: Group by Drug Interaction ($M \pm SE$)

There was also a significant group by session interaction ($F(4, 80) = 5.877$, $p < .001$, $\eta_p^2 = .227$). Post hoc analyses indicated that the fatigue-resistant group performed significantly better than the fatigue-vulnerable group at all sessions. Within the fatigue-resistant group, the baseline session was significantly better than sessions 2 through 4; session 1 was significantly better than

session 2. Within the fatigue-vulnerable group, the baseline session and session 1 were significantly better than sessions 2 through 4. This effect is shown in Figure 88.

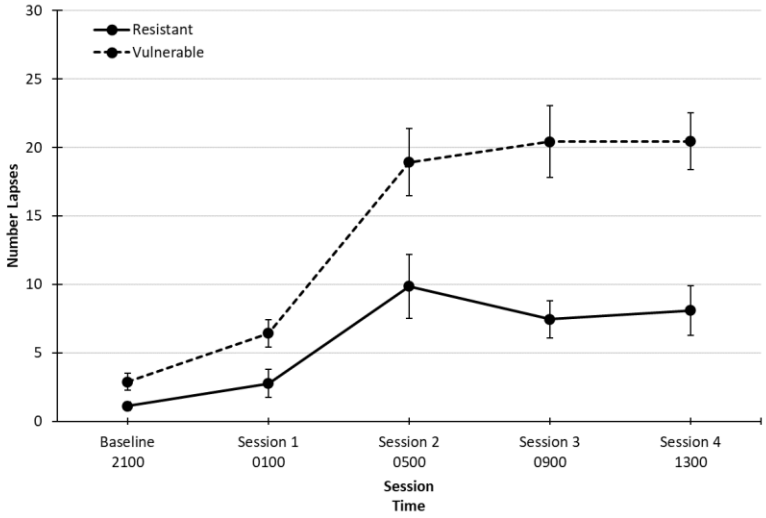


Figure 88. PVT Lapses: Group by Session Interaction ($M \pm SE$)

The assumption of sphericity was violated for the drug by session interaction ($\chi^2(9) = 21.896$, $p = .009$, $\varepsilon = .903$). The repeated measures ANOVA showed a significant two-way interaction between drug and session ($F(3.613, 72.256) = 12.150$, $p < .001$, $\eta_p^2 = .378$). Post hoc comparisons indicated that performance was better during the modafinil condition than during the placebo condition at sessions 2 and 3. For the modafinil condition, the baseline session performance was significantly better than sessions 2 through 4; session 1 was significantly better than session 4. For the placebo condition, the baseline session performance was significantly better than sessions 2 through 4; session 1 was significantly better than sessions 2 through 4. These effects are shown in Figure 89.

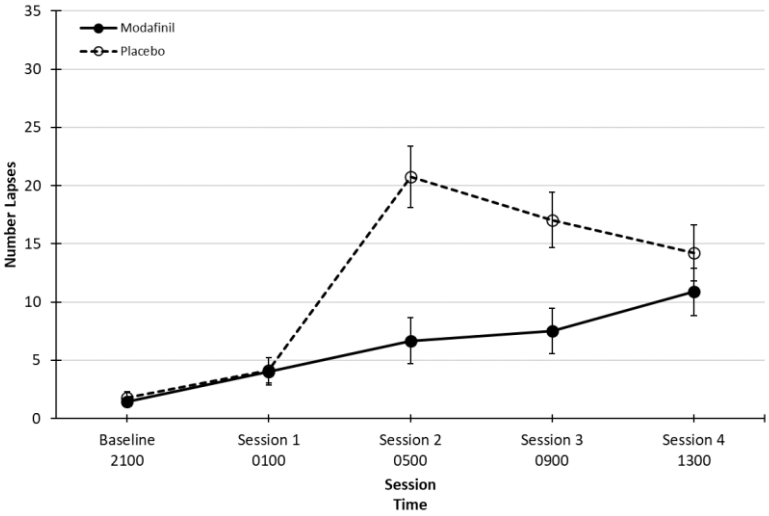


Figure 89. PVT Lapses: Drug by Session Interaction ($M \pm SE$)

The main effect for group was significant ($F(1, 20) = 24.582$, $p < .001$, $\eta_p^2 = .551$), with fewer lapses in the fatigue-resistant compared to the fatigue-vulnerable group. The means (*SE*) for the resistant and vulnerable groups were 5.850 (1.187) and 13.817 (1.083), respectively.

The main effect for drug was significant ($F(1, 20) = 26.779$, $p < .001$, $\eta_p^2 = .572$), with performance following administration of modafinil better than performance following administration of placebo. The means (*SE*) for the modafinil and placebo conditions were 7.193 (1.117) and 12.473 (0.751), respectively.

The assumption of sphericity was violated for the main effect for session ($\chi^2(9) = 25.490$, $p = .003$, $\varepsilon = .781$). The main effect for session was significant ($F(3.125, 62.502) = 33.633$, $p < .001$, $\eta_p^2 = .627$). Post hoc comparisons indicated that baseline session and session 1 performance were better than sessions 2 through 4. This pattern is shown in Figure 90.

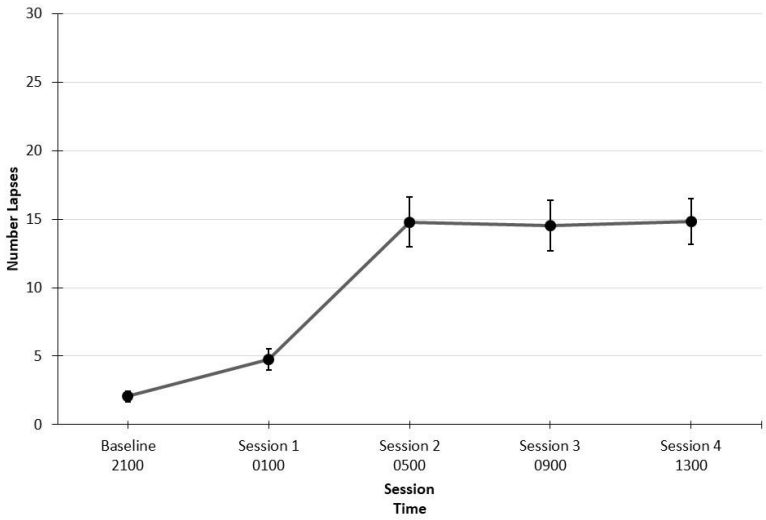


Figure 90. PVT Lapses: Session Main Effect (*M* ± *SE*)

RRT: The grouping resulted in 11 individuals in the fatigue-resistant group and 11 in the fatigue-vulnerable group. The average (*SD*) hours of sleep obtained the 3 nights before the placebo visit to the lab were 8.25 (0.46) for the fatigue-resistant group and 8.33 (0.60) for the fatigue-vulnerable group ($t(16) = 0.055$, $p = .957$).

There was not a significant three-way interaction between group, drug, and session ($F(4, 80) = 1.394$, $p = .243$, $\eta_p^2 = .065$) nor significant two-way interactions between group and session ($F(4, 80) = 1.374$, $p = .250$, $\eta_p^2 = .064$) or group and drug ($F(1, 20) = 0.994$, $p = .331$, $\eta_p^2 = .047$). Figure 91 shows the relationship among group, drug, and session.

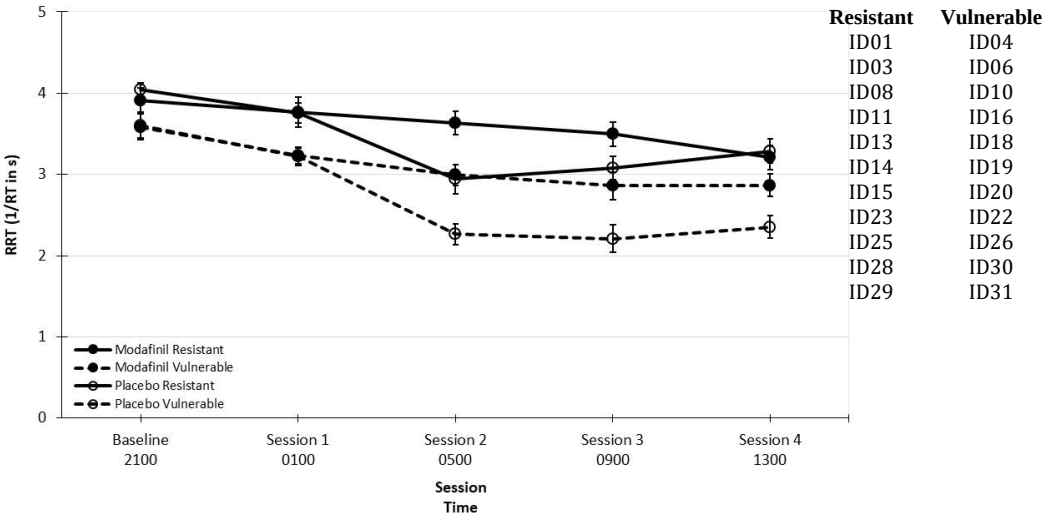


Figure 91. PVT RRT: Group by Drug by Session Interaction ($M \pm SE$)

There was a significant two-way interaction between drug and session ($F(4, 80) = 11.248$, $p < .001$, $\eta_p^2 = .360$). Post hoc comparisons indicated that performance during the modafinil condition was better than during the placebo condition at sessions 2 and 3. For the modafinil condition, the baseline session performance was significantly better than all other sessions; session 1 was significantly better than sessions 2 through 4; and session 2 was significantly better than session 4. For the placebo condition, the baseline session performance was significantly better than all other sessions; session 1 was significantly better than sessions 2 through 4. These effects are illustrated in Figure 92.

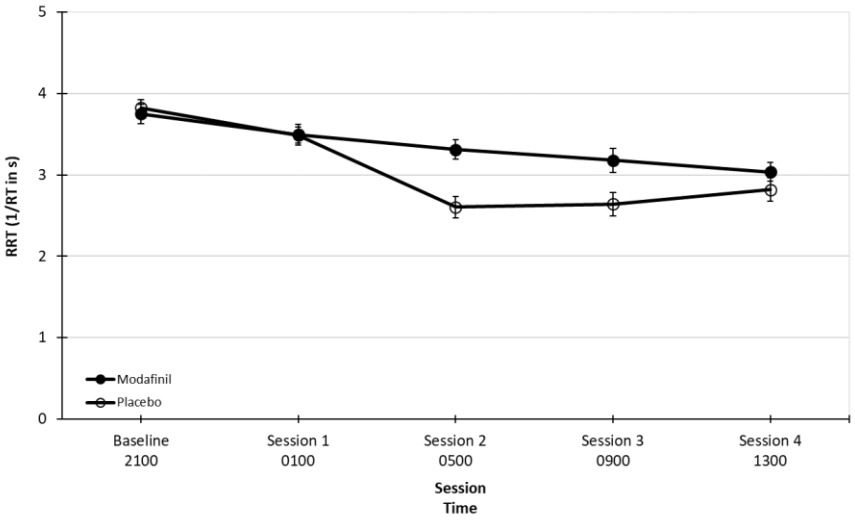


Figure 92. PVT RRT: Drug by Session Interaction ($M \pm SE$)

The main effect for group was significant ($F(1, 20) = 19.795$, $p < .001$, $\eta_p^2 = .497$), with performance for the fatigue-resistant group better than performance for the fatigue-vulnerable

group. The means (*SE*) for the resistant and vulnerable groups were 3.512 (0.094) and 2.918 (0.094), respectively.

The main effect for drug was significant ($F(1, 20) = 7.986$, $p = .010$, $\eta_p^2 = .285$), with performance following administration of modafinil better than performance following administration of placebo. The means (*SE*) for the modafinil and placebo conditions were 3.354 (0.098) and 3.075 (0.065), respectively.

The assumption of sphericity was violated for the main effect for session ($\chi^2(9) = 17.230$, $p = .046$, $\varepsilon = .829$).The main effect for session was significant ($F(3.314, 66.283) = 45.575$, $p < .001$, $\eta_p^2 = .695$). Post hoc comparisons indicated that the baseline session performance was better than all other sessions; session 1 performance was better than sessions 2 through 4. This pattern is shown in Figure 93.

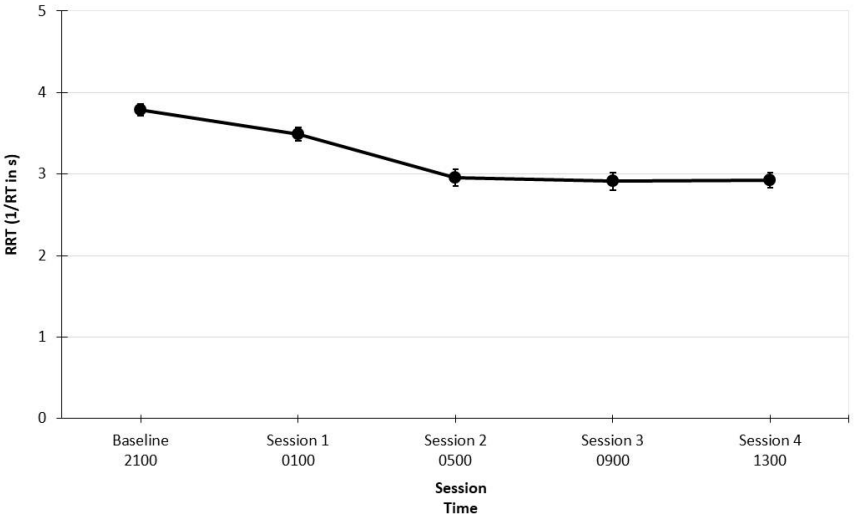


Figure 93. PVT RRT: Session Main Effect ($M \pm SE$)

3.2.1.2 The Stroop Task (NTI ATS™).

The analyses for the Stroop Task included metrics for number correct (NCorr) and the average RT for the number of correct responses (CorrRT) for the incongruent stimuli. One participant scored more than 3 standard deviations from the mean during his baseline session and was thus excluded as an outlier from all analyses, leaving a final sample size of 21.

Incongruent NCorr: The grouping for this metric resulted in 12 individuals in the fatigue-resistant group and 9 in the fatigue-vulnerable group. The average (*SD*) hours of sleep obtained the 3 nights before the placebo visit to the lab were 8.45 (0.55) for the fatigue-resistant group and 8.02 (0.37) for the fatigue-vulnerable group ($t(19) = 2.019$, $p = .058$).

The repeated measures ANOVA showed a significant three-way interaction among group, drug, and session ($F(4, 76) = 5.486$, $p = .001$, $\eta_p^2 = .224$). Post hoc analyses indicated significant

differences between the groups within the modafinil condition at sessions 3 and 4, and within the placebo condition at sessions 2, 3, and 4. The effect is illustrated in Figure 94 below.

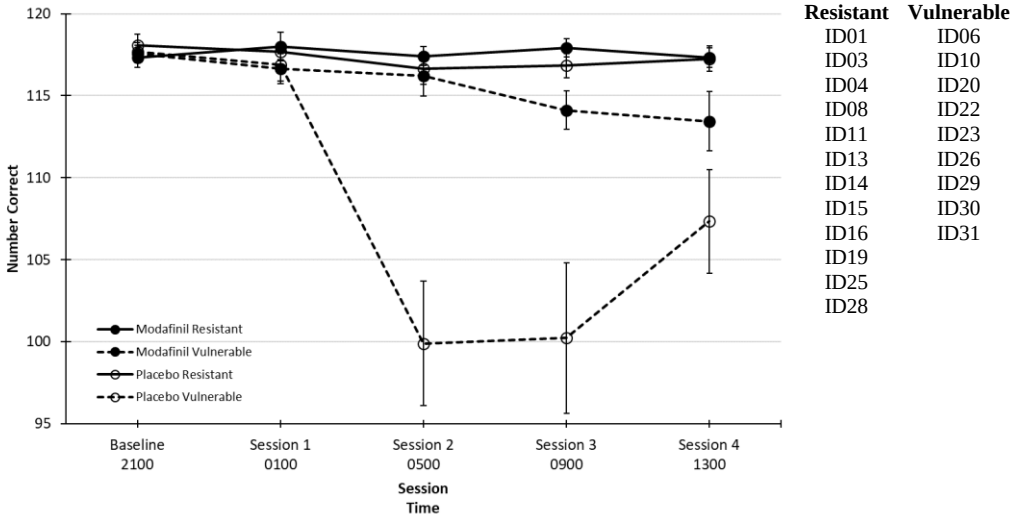


Figure 94. Stroop Task Incongruent NCorr: Group by Drug by Session Interaction ($M \pm SE$)

There was a significant two-way interaction between group and drug ($F(1, 19) = 38.296$, $p < .001$, $\eta_p^2 = .668$). Post hoc analyses indicated differences between the groups for both modafinil and placebo conditions. Additionally, there were significant differences in performance between the modafinil and placebo conditions within the fatigue-vulnerable group, but not within the fatigue-resistant group. These comparisons are shown in Figure 95 below.

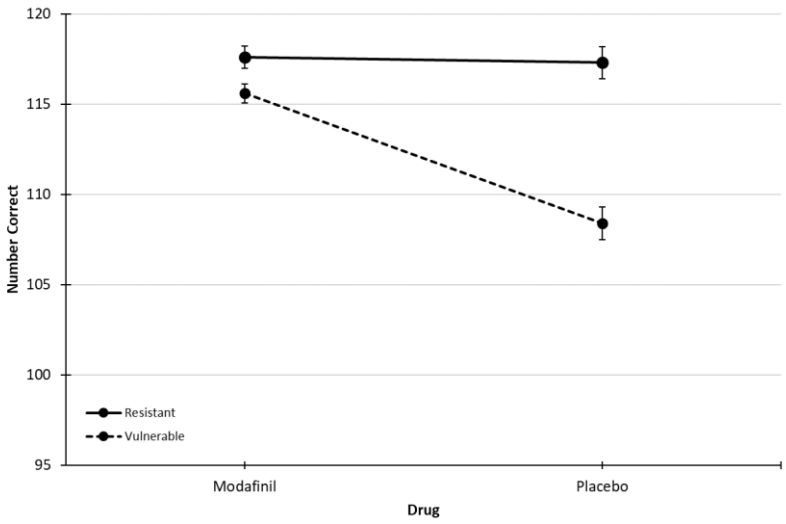


Figure 95. Stroop Task Incongruent NCorr: Group by Drug Interaction ($M \pm SE$)

There was a significant interaction between group and session ($F(4, 76) = 9.445$, $p < .001$, $\eta_p^2 = .332$). Post hoc analyses revealed differences between the groups at sessions 2 through 4, with the resistant group showing better performance at these sessions than the vulnerable group.

Within the fatigue-resistant group, no sessions were significantly different. Within the fatigue-vulnerable group, baseline session and session 1 performance were significantly better than sessions 2 through 4. The effects are illustrated in Figure 96 below.

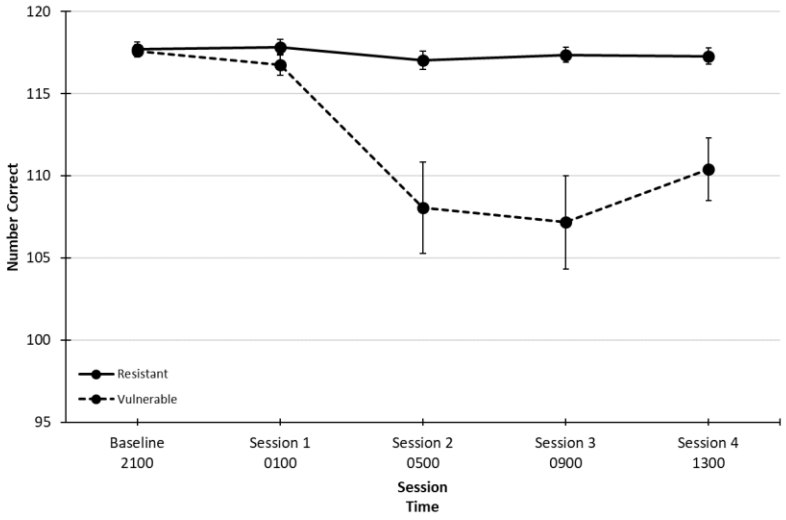


Figure 96. Stroop Task Incongruent NCorr: Group by Session Interaction ($M \pm SE$)

The assumption of sphericity was violated for the drug by session interaction ($\chi^2(9) = 46.125$, $p < .001$, $\varepsilon = .526$). There was a significant drug by session interaction ($F(2.103, 39.950) = 7.300$, $p = .002$, $\eta_p^2 = .278$). Post hoc analyses revealed significant differences between the two drug conditions at sessions 2 and 3, with modafinil showing better performance at these sessions compared to placebo. There were no differences between the sessions within the modafinil condition. Within the placebo condition, the baseline session performance was significantly better than sessions 2 through 4; session 1 was significantly better than sessions 2 and 3. Results are shown in Figure 97.

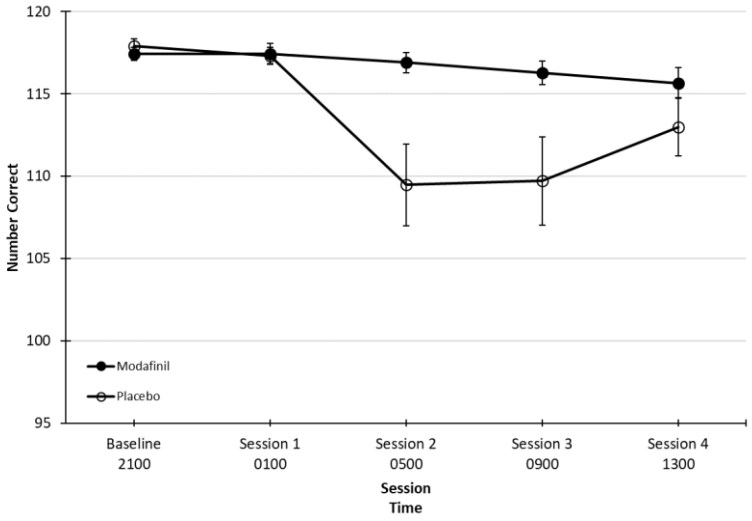


Figure 97. Stroop Task Incongruent NCorr: Drug by Session Interaction ($M \pm SE$)

There was a significant main effect for group ($F(1,19) = 45.945$, $p < .001$, $\eta_p^2 = .707$). Performance within the fatigue-resistant group was better overall than performance within the fatigue-vulnerable group. The means (*SE*) for the resistant and vulnerable groups were 117.450 (0.526) and 112.000 (0.608), respectively.

The main effect for drug was significant ($F(1, 19) = 45.246$, $p < .001$, $\eta_p^2 = .704$, with performance following administration of modafinil better than performance following administration of placebo. The means (*SE*) for the modafinil and placebo conditions were 116.600 (0.417) and 112.850 (0.552), respectively.

The assumption of sphericity was violated for the session main effect ($\chi^2(9) = 53.198$, $p < .001$, $\varepsilon = .500$). The main effect for session was significant ($F(2.001, 38.010) = 11.888$, $p < .001$, $\eta_p^2 = .385$). Pairwise comparisons between means indicated the baseline session and session 1 performance were significantly better than sessions 2 through 4. This effect is illustrated in Figure 98 below.

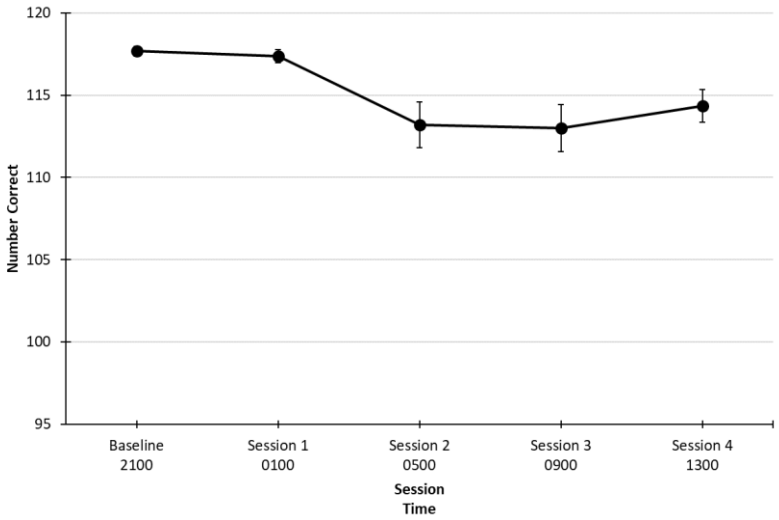


Figure 98. Stroop Task Incongruent NCorr: Session Main Effect ($M \pm SE$)

Incongruent CorrRT: The grouping for this metric resulted in 10 individuals in the fatigue-resistant group and 11 in the fatigue-vulnerable group. The average (*SD*) hours of sleep obtained the 3 nights before the placebo visit to the lab were 8.16 (0.51) for the fatigue-resistant group and 8.36 (0.54) for the fatigue-vulnerable group ($t(19) = -0.895$, $p = .382$).

There was not a significant three-way interaction among group, drug, and session ($F(4, 76) = 0.641$, $p = .635$, $\eta_p^2 = .033$). Figure 99 shows the relationship among group, drug, and session.

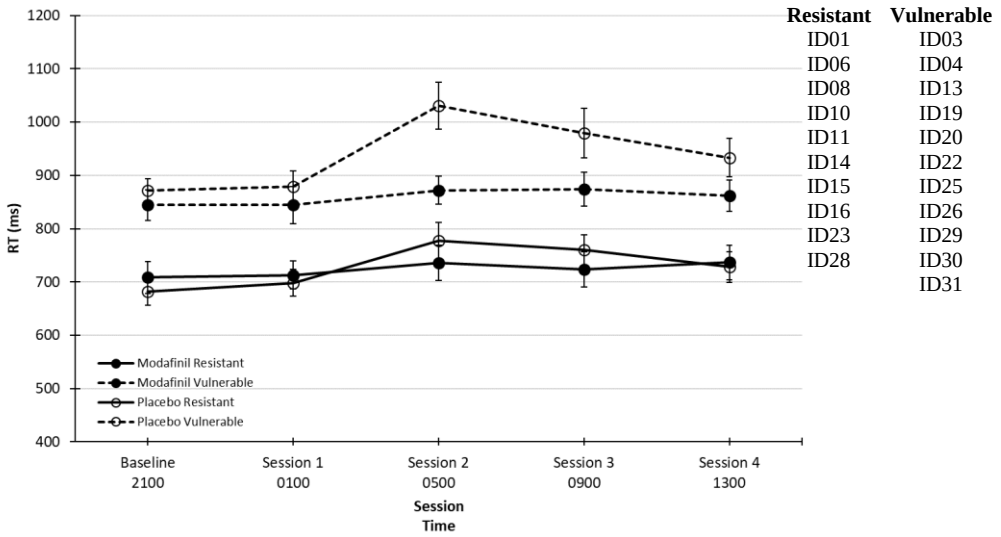


Figure 99. Stroop Task Incongruent CorrRT: Group by Drug by Session Interaction ($M \pm SE$)

There was a significant two-way interaction between group and drug ($F(1, 19) = 7.506$, $p = .013$, $\eta_p^2 = .283$). Post hoc analyses indicated differences between the groups for both modafinil and placebo conditions, with the fatigue-resistant group outperforming the fatigue-vulnerable group. Additionally, there were differences in performance between modafinil and placebo conditions within the fatigue-vulnerable group, with faster performance during the modafinil condition than the placebo condition; there were no differences between the conditions within the fatigue-resistant group. These comparisons are shown in Figure 100.

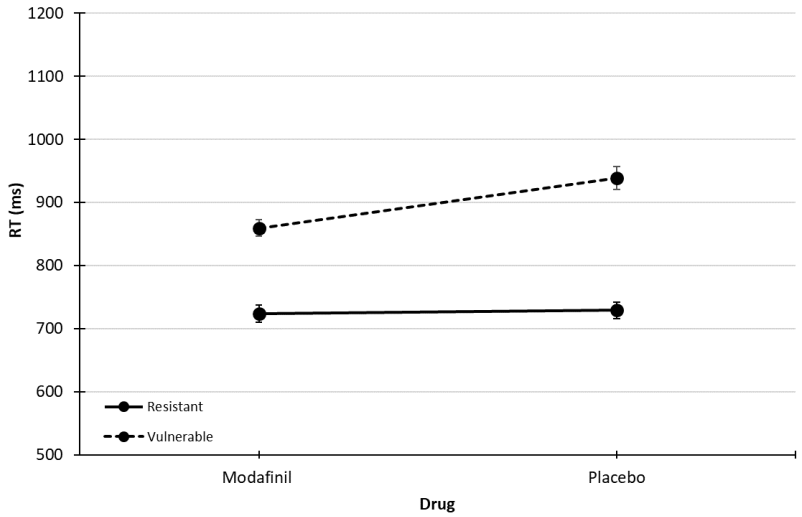


Figure 100. Stroop Task Incongruent CorrRT: Group by Drug Interaction ($M \pm SE$)

There was not a significant interaction between group and session ($F(4, 76) = 0.579$, $p = .679$, $\eta_p^2 = .030$).

The assumption of sphericity was violated for the drug by session interaction ($\chi^2(9) = 19.090$, $p = .025$, $\varepsilon = .888$). There was a significant drug by session interaction ($F(3.550, 67.456) = 6.184$, $p < .001$, $\eta_p^2 = .246$). Post hoc analyses revealed significant differences between the two drug conditions at sessions 2 and 3, with modafinil showing faster performance at these sessions compared to placebo. There were no differences between sessions within the modafinil condition. Within the placebo condition, the baseline session and session 1 performance were significantly faster than sessions 2 through 4; session 2 was significantly slower than sessions 3 and 4. Results are shown in Figure 101.

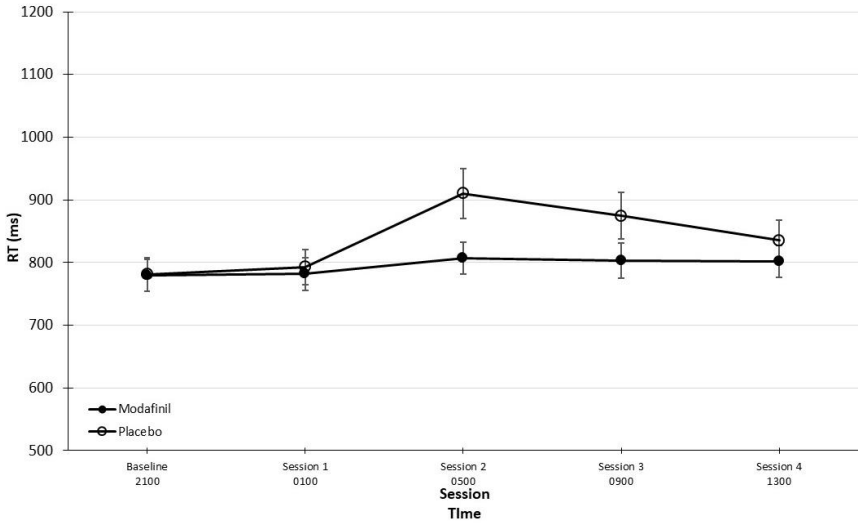


Figure 101. Stroop Task Incongruent CorrRT: Drug by Session Interaction ($M \pm SE$)

There was a significant main effect for group ($F(1,19) = 23.344$, $p < .001$, $\eta_p^2 = .551$). Performance within the fatigue-resistant group was faster overall than performance within the fatigue-vulnerable group. The mean (*SE*) reaction times for the resistant and vulnerable groups were 726.148 (25.901) and 899.056 (24.695), respectively.

The main effect for drug was significant ($F(1, 19) = 9.857$, $p = .005$, $\eta_p^2 = .342$. The means (*SE*) for the modafinil and placebo conditions were 791.356 (19.794) and 833.848 (18.443), respectively.

The main effect for session was significant ($F(4, 76) = 9.276$, $p < .001$, $\eta_p^2 = .328$). Post hoc analyses indicated the baseline session and session 1 were significantly faster than sessions 2 through 4; session 2 was significantly slower than session 4. This effect is illustrated in Figure 102 below.

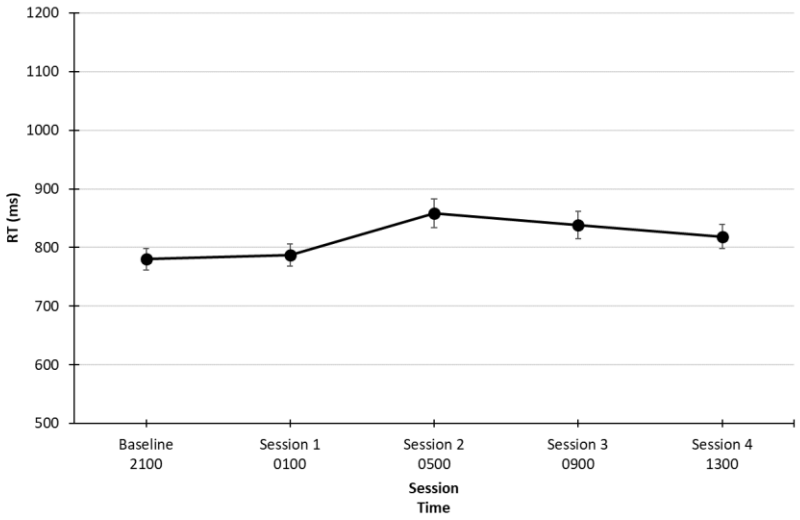


Figure 102. Stroop Task Incongruent CorrRT: Session Main Effect (*M* ± *SE*)

3.2.1.3 Rapid Decision Making Task (NTI ATS™).

The analyses for the Rapid Decision Making Task included metrics for number of correct responses (NCorr) and the average reaction time for the number of correct responses (CorrRT).

NCorr: The grouping resulted in 11 individuals in the fatigue-resistant group and 11 in the fatigue-vulnerable group. The average (*SD*) hours of sleep obtained the 3 nights before the placebo visit to the lab were 8.32 (0.50) for the fatigue-resistant group and 8.23 (0.54) for the fatigue-vulnerable group ($t(20) = 0.374$, $p = .712$).

There was not a significant group by drug by session interaction ($F(4, 80) = 0.466$, $p = .761$, $\eta_p^2 = .023$), a significant group by drug interaction ($F(1, 20) = 0.235$, $p = .633$, $\eta_p^2 = .012$), nor a significant group by session interaction ($F(4, 80) = 2.365$, $p = .060$, $\eta_p^2 = .106$). The assumption of sphericity was violated for the drug x session interaction ($\chi^2(9) = 45.879$, $p < .001$, $\varepsilon = .506$). The interaction between drug and session was not significant ($F(2.025, 40.500) = 2.867$, $p = .068$, $\eta_p^2 = .125$). Figure 103 illustrates the relationship among group, drug, and session.

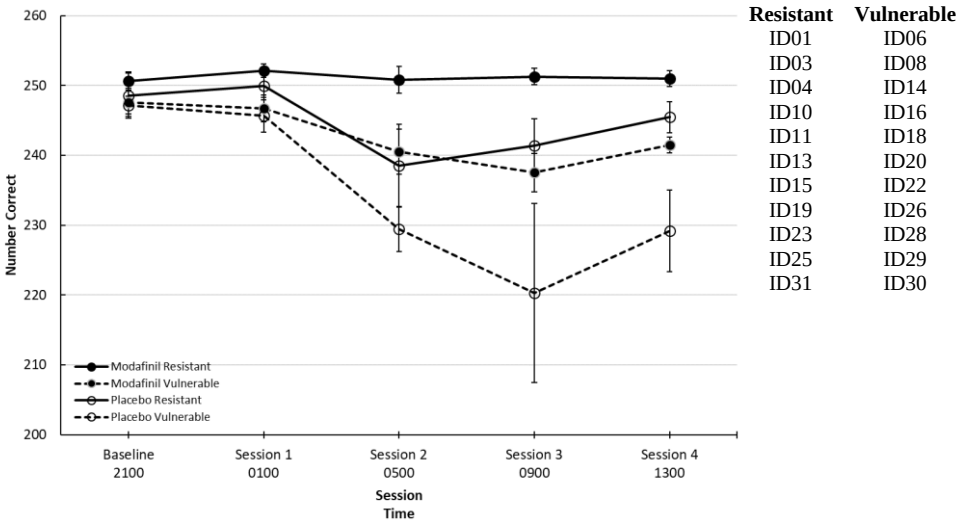


Figure 103. RDMT NCorr: Group by Drug by Session Effect ($M \pm SE$)

The main effect for group was significant ($F(1, 20) = 14.923$, $p = .001$, $\eta_p^2 = .427$), with performance for the fatigue-resistant group better than performance for the fatigue-vulnerable group. The means (*SE*) for the resistant and vulnerable groups were 247.964 (1.722) and 238.555 (1.722), respectively.

The main effect for drug was significant ($F(1, 20) = 12.691$, $p = .002$, $\eta_p^2 = .388$, with performance during the modafinil condition better than performance during the placebo condition. The means (*SE*) for the modafinil and placebo conditions were 246.964 (0.789) and 239.555 (2.123), respectively.

The assumption of sphericity was violated for session ($\chi^2(9) = 50.708$, $p < .001$, $\varepsilon = .574$). There was a significant main effect for session ($F(2.295, 45.898) = 6.439$, $p = .002$, $\eta_p^2 = .244$). Post hoc comparisons indicated that the baseline session and session 1 performance were significantly better than sessions 2 through 4. This effect is shown in Figure 104.

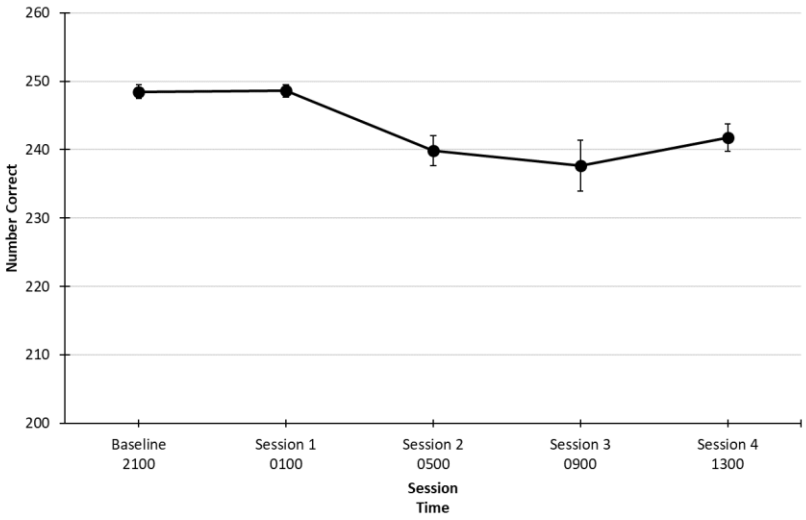
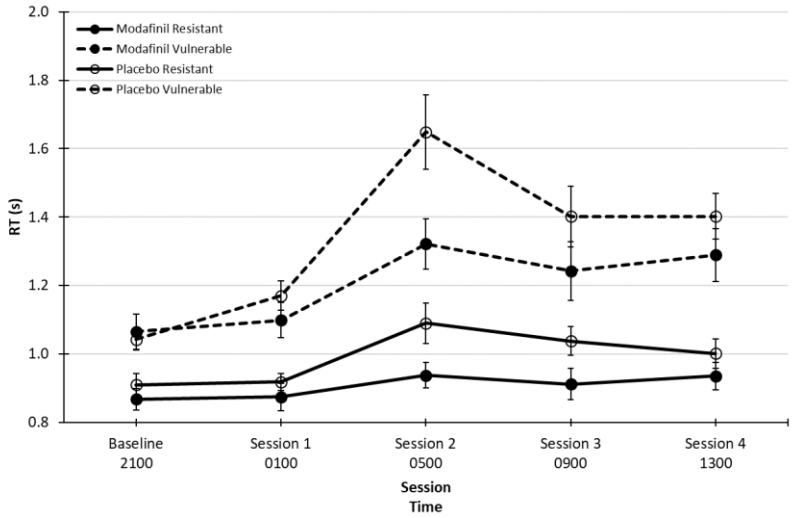


Figure 104. RDMT NCorr: Session Main Effect (*M* ± *SE*)

CorrRT: The grouping resulted in 11 individuals in the fatigue-resistant group and 11 in the fatigue-vulnerable group. The average (*SD*) hours of sleep obtained the 3 nights before the placebo visit to the lab were 8.23 (0.39) for the fatigue-resistant group and 8.33 (0.63) for the fatigue-vulnerable group ($t(20) = -0.442$, $p = .663$).

There was not a significant group by drug by session interaction ($F(4, 80) = 1.437$, $p = .229$, $\eta_p^2 = .067$) nor a significant group by drug interaction ($F(1, 20) = 0.551$, $p = .466$, $\eta_p^2 = .027$). Figure 105 illustrates the relationship among group, drug, and session.



Resistant	Vulnerable
ID01	ID04
ID03	ID06
ID08	ID14
ID10	ID18
ID11	ID19
ID13	ID22
ID15	ID23
ID16	ID26
ID20	ID29
ID25	ID30
ID28	ID31

Figure 105. RDMT CorrRT: Group by Drug by Session Interaction (*M* ± *SE*)

There was a significant group by session interaction ($F(4, 80) = 7.362$, $p < .001$, $\eta_p^2 = .269$). Post hoc comparisons indicated faster performance for the fatigue-resistant group than the fatigue-vulnerable group at all sessions. Within the resistant group, the baseline session was significantly

faster than sessions 2 and 4 and marginally faster than session 3 (p = .053). Within the vulnerable group, the baseline session was significantly faster than all other sessions; session 1 was significantly faster than sessions 2 through 4; session 2 also was significantly slower than sessions 3 and 4. This effect is illustrated in Figure 106.

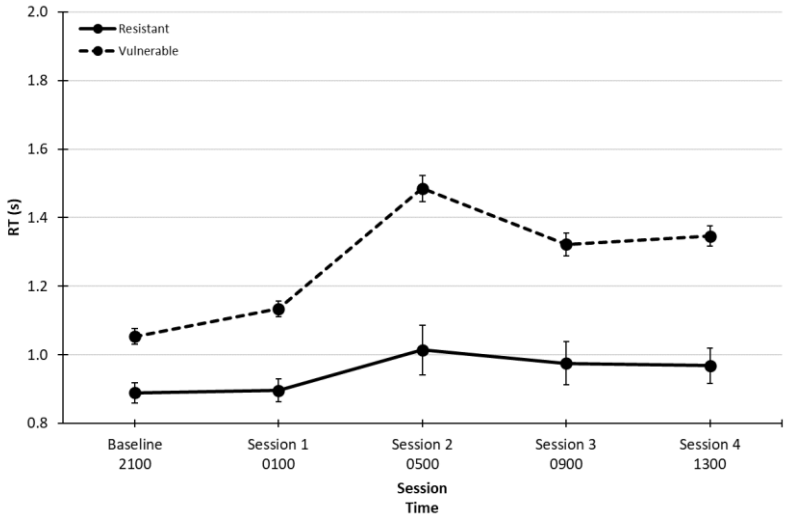


Figure 106. RDMT CorrRT: Group by Session Interaction ($M \pm SE$)

The assumption of sphericity was violated for the drug by session interaction ($\chi^2(9) = 21.185$, $p = .012$, $\varepsilon = .878$). The interaction between drug and session was significant ($F(3.512, 70.233) = 6.139$, $p < .001$, $\eta_p^2 = .235$). Post hoc analyses indicated differences between the two drugs at sessions 1 through 4 such that reaction times were faster in the modafinil condition compared to placebo. Within the modafinil condition, the baseline session and session 1 were significantly faster than sessions 2 through 4. Within the placebo condition, the baseline session was significantly faster than all other sessions; session 1 was significantly faster than sessions 2 through 4; session 2 also was significantly slower than sessions 3 and 4. These effects are illustrated in Figure 107.

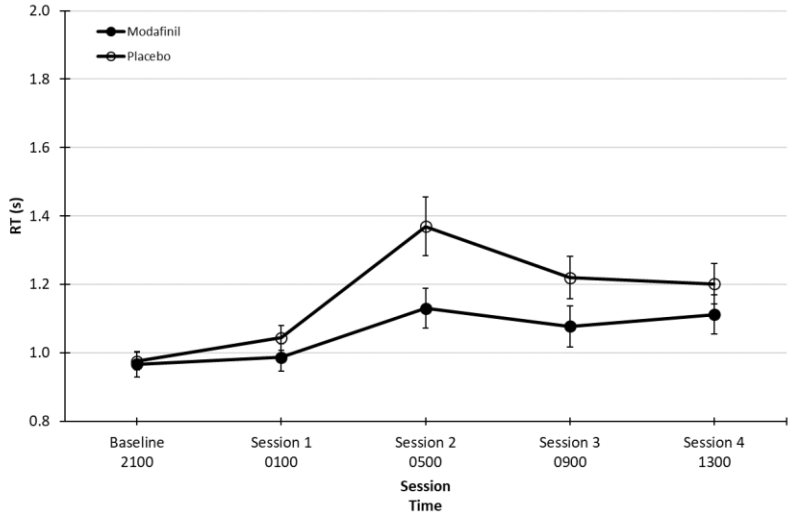


Figure 107. RDMT CorrRT: Drug by Session Interaction ($M \pm SE$)

The main effect for group was significant ($F(1, 20) = 30.729$, $p < .001$, $\eta_p^2 = .606$), with performance for the fatigue-resistant group faster than performance for the fatigue-vulnerable group. The means (*SE*) for the resistant and vulnerable groups were 0.948 (0.041) and 1.268 (0.041), respectively.

The main effect for drug was significant ($F(1, 20) = 13.754$, $p = .001$, $\eta_p^2 = .407$, with performance for the modafinil condition faster than performance for the placebo condition. The means (*SE*) for the modafinil and placebo conditions were 1.054 (0.034) and 1.162 (0.030), respectively.

The assumption of sphericity was violated for session ($\chi^2(9) = 20.464$, $p = .016$, $\varepsilon = .879$). There was a significant main effect for session ($F(3.514, 70.282) = 26.153$, $p < .001$, $\eta_p^2 = .567$). Post hoc comparisons indicated that the baseline session was significantly faster than all other sessions; session 1 was significantly faster than sessions 2 through 4; session 2 also was significantly slower than sessions 3 and 4. This effect is shown in Figure 108.

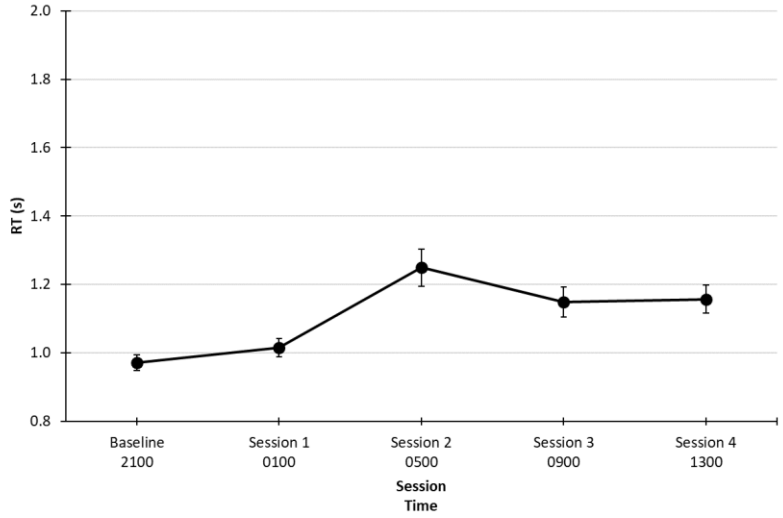


Figure 108. RDMT CorrRT: Session Main Effect (*M* ± *SE*)

3.2.1.4 Delayed Match to Sample Task (NTI ATS™).

The analyses for the Delayed Match to Sample Task included metrics for number of correct responses (NCorr) and the average reaction time for the number of correct responses (CorrRT).

NCorr: The grouping resulted in 10 individuals in the fatigue-resistant group and 12 in the fatigue-vulnerable group. The average (*SD*) hours of sleep obtained the 3 nights before the placebo visit to the lab were 8.33 (0.54) for the fatigue-resistant group and 8.23 (0.50) for the fatigue-vulnerable group ($t(20) = 0.466$, $p = .646$).

The repeated measures ANOVA showed a significant three-way interaction among group, drug, and session ($F(4, 80) = 6.149$, $p < .001$, $\eta_p^2 = .235$). Post hoc analyses indicated differences within the modafinil condition between the two groups at baseline and approached significance at session 4 ($p = .055$), with the fatigue-resistant group outperforming the fatigue-vulnerable group. There were also differences between the two groups within the placebo condition at sessions 1, 2, and 3, with the fatigue-resistant group again outperforming the fatigue-vulnerable group. Within the fatigue-resistant group, there were no differences between sessions after administration of either modafinil or placebo. Within the fatigue-vulnerable group, after modafinil administration, the baseline session and session 1 performance were better than session 4; session 3 was better than session 4. After placebo administration, the baseline session was significantly better than all sessions; session 1 was significantly better than sessions 2 and 3; and sessions 2 and 3 performance were significantly worse than session 4. Within the fatigue-resistant group, performance after modafinil administration was no different than after placebo administration within any session. Within the fatigue-vulnerable group, performance after modafinil administration was significantly better than performance after placebo administration at sessions 2 and 3. These effects are illustrated in Figure 109 below.

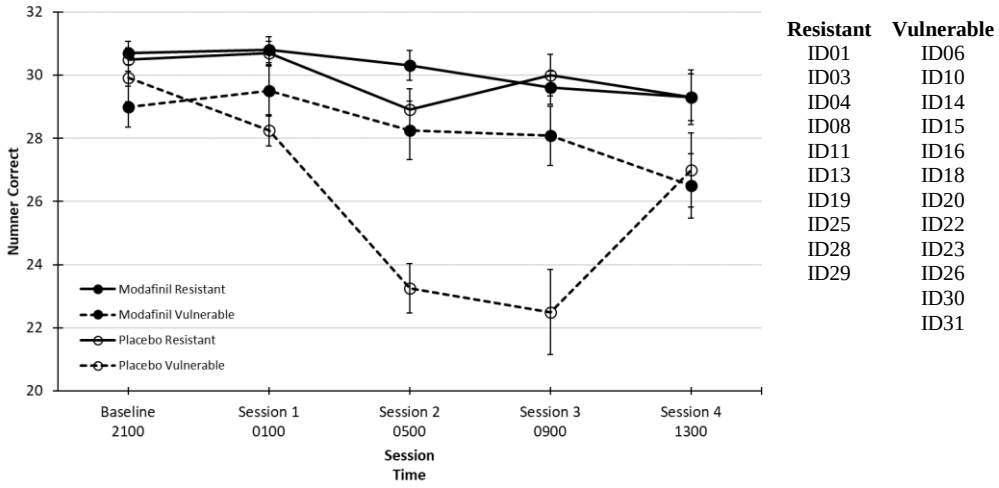


Figure 109. DMTS NCorr: Group by Drug by Session Interaction ($M \pm SE$)

There was a significant interaction between group and drug ($F(1, 20) = 5.771$, $p = .026$, $\eta_p^2 = .224$). Post hoc analyses revealed significant differences between the two groups after administration of both modafinil and placebo. Within the fatigue-resistant group, there was no difference between the drugs; within the fatigue-vulnerable group, modafinil administration produced better performance than placebo administration. Results are shown in Figure 110.

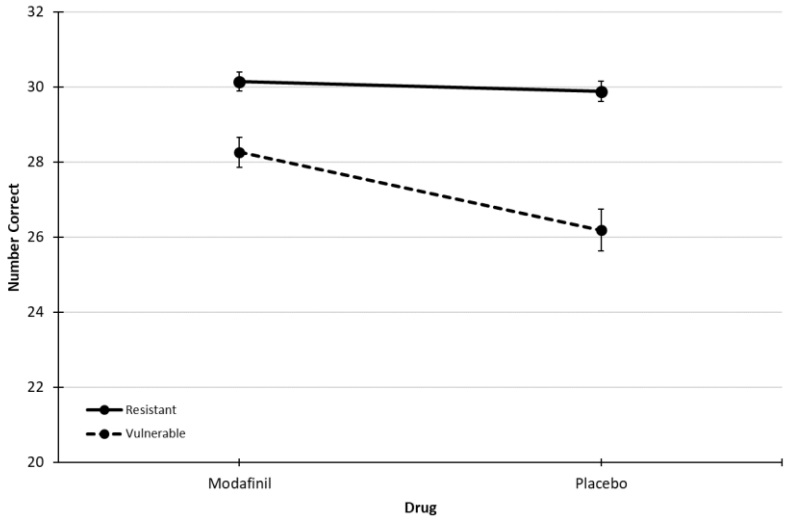


Figure 110. DMTS NCorr: Group by Drug Interaction ($M \pm SE$)

There was a significant interaction between group and session ($F(4, 80) = 3.430$, $p = .012$, $\eta_p^2 = .146$). Post hoc analyses revealed significant differences between the two groups at sessions 1 through 4, with the fatigue-resistant group showing better performance than the fatigue-vulnerable group. Within the fatigue-resistant group, there were no significant differences between the sessions, with performance remaining relatively steady. Within the fatigue-vulnerable group, the baseline session and session 1 had significantly better performance compared to sessions 2 through 4. Results are shown in Figure 111.

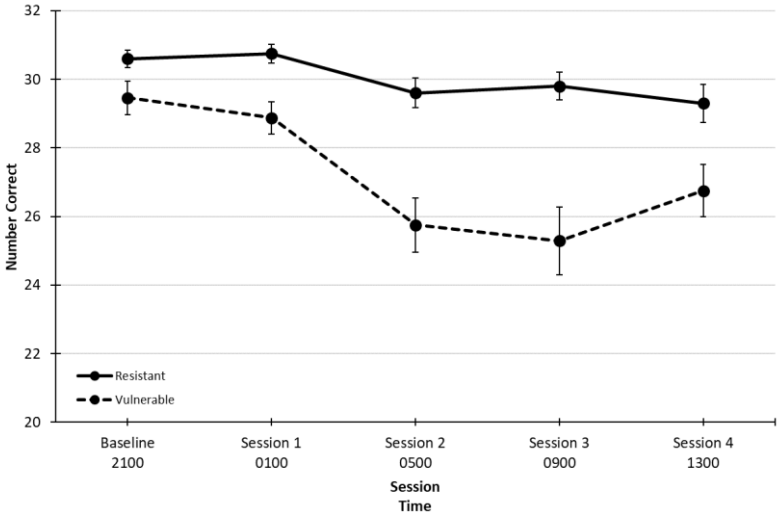


Figure 111. DMTS NCorr: Group by Session Interaction ($M \pm SE$)

Mauchly's Test of Sphericity was violated for the drug by session interaction ($\chi^2(9) = 21.866$, $p = .010$, $\varepsilon = .859$). There was a significant interaction between drug and session ($F(3.438, 68.753) = 7.556$, $p < .001$, $\eta_p^2 = .274$). Post hoc analyses revealed significant differences between the two drugs at sessions 2 and 3, with modafinil administration maintaining performance better than placebo administration. Within the modafinil condition, the baseline session and session 1 performance were significantly better than sessions 3 and 4. Within the placebo condition, the baseline session performance was significantly better than sessions 2 through 4; session 1 was significantly better than sessions 2 and 3; and session 2 was significantly worse than session 4. Results are shown in Figure 112.

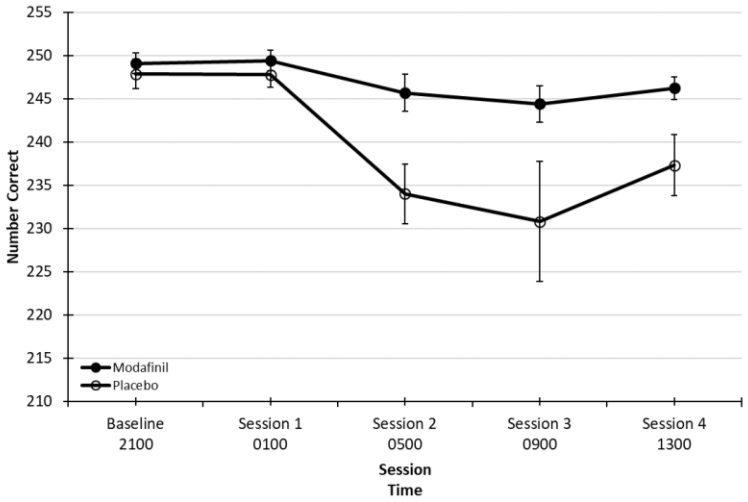


Figure 112. DMTS NCorr: Drug by Session Interaction ($M \pm SE$)

There was a significant main effect for group ($F(1, 20) = 18.832$, $p < .001$, $\eta_p^2 = .485$). The fatigue-resistant group had better overall performance than the fatigue-vulnerable group. The

means (*SE*) for the resistant and vulnerable groups were 30.010 (0.474) and 27.225 (0.433), respectively.

There was a significant main effect for drug ($F(1, 20) = 9.533$, $p = .006$, $\eta_p^2 = .323$). Performance after modafinil administration was significantly better than performance after placebo administration. The means (*SE*) for the modafinil and placebo conditions were 29.203 (0.371) and 28.032 (0.375), respectively.

There was a significant main effect for session ($F(4, 80) = 10.367$, $p < .001$, $\eta_p^2 = .341$). The baseline session and session 1 performance were significantly better than sessions 2 through 4. The effect is illustrated in Figure 113.

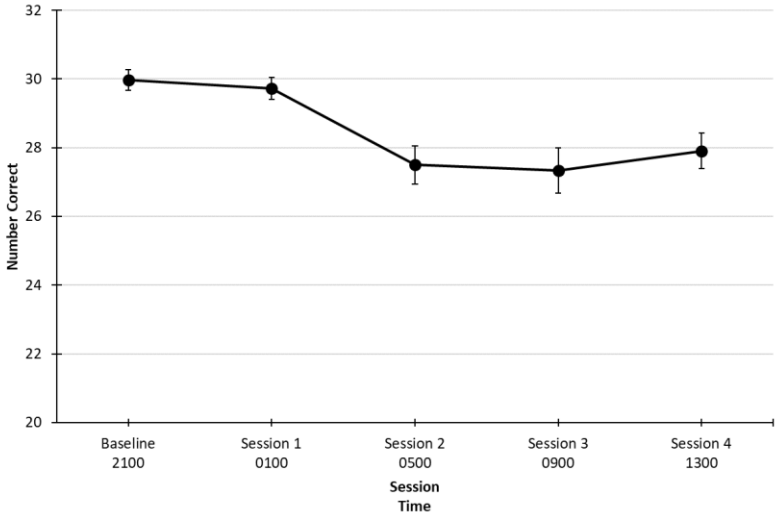


Figure 113. DMTS NCorr: Session Main Effect (*M* ± *SE*)

CorrRT: The grouping resulted in 11 individuals in the fatigue-resistant group and 11 in the fatigue-vulnerable group. The average (*SD*) hours of sleep obtained the 3 nights before the placebo visit to the lab were 8.24 (0.42) for the fatigue-resistant group and 8.31 (0.61) for the fatigue-vulnerable group ($t(20) = -0.305$, $p = .763$).

There was not a significant group by drug by session interaction ($F(4, 80) = 0.108$, $p = .979$, $\eta_p^2 = .005$), a significant group by drug interaction ($F(1, 20) = 0.037$, $p = .850$, $\eta_p^2 = .002$), a significant group by session interaction ($F(4, 80) = 2.237$, $p = .072$, $\eta_p^2 = .101$), nor a drug by session interaction ($F(4, 80) = 0.716$, $p = .583$, $\eta_p^2 = .035$). Figure 114 illustrates the relationship among group, drug, and session.

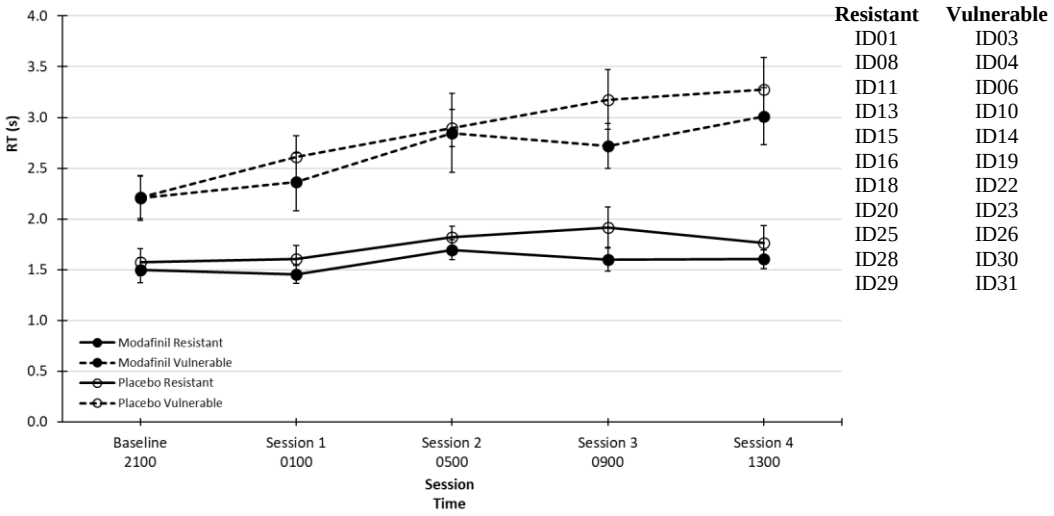


Figure 114. DMTS CorrRT: Group by Drug by Session Interaction ($M \pm SE$)

There was a significant main effect for group ($F(1, 20) = 39.117$, $p < .001$, $\eta_p^2 = .662$). The fatigue-resistant group had better overall performance than the fatigue-vulnerable group. The means (*SE*) for the resistant and vulnerable groups were 1.653 (0.122) and 2.732 (0.122), respectively.

There was not a significant main effect for drug ($F(1, 20) = 3.643$, $p = .071$, $\eta_p^2 = .154$). The means (*SE*) for the modafinil and placebo conditions were 2.101 (0.101) and 2.285 (0.097), respectively.

There was a significant main effect for session ($F(4, 80) = 6.077$, $p < .001$, $\eta_p^2 = .233$). The baseline session and session 1 performance were significantly better than sessions 2 through 4. The effect is illustration in Figure 115.

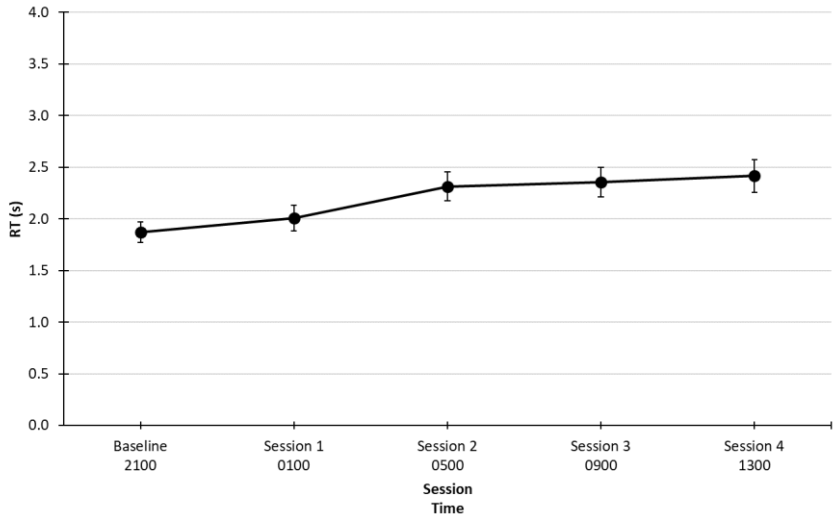


Figure 115. DMTS CorrRT: Session Main Effect ($M \pm SE$)

3.2.1.5 The Wisconsin Card Sorting Task (WCST).

The analyses for the Wisconsin Card Sorting Task included metrics for perseverative errors (PE) and failures to maintain set (FMS).

PE: The grouping resulted in 10 individuals in the fatigue-resistant group and 12 in the fatigue-vulnerable group. The average (*SD*) hours of sleep obtained the 3 nights before the placebo visit to the lab were 8.31 (0.55) for the fatigue-resistant group and 8.25 (0.50) for the fatigue-vulnerable group ($t(20) = 0.260$, $p = .797$).

There was not a significant group by drug by session interaction ($F(4, 80) = 0.790$, $p = .535$, $\eta_p^2 = .038$), a significant group by drug interaction ($F(1, 20) = 3.888$, $p = .063$, $\eta_p^2 = .163$), nor a significant group by session interaction ($F(4, 80) = 0.716$, $p = .583$, $\eta_p^2 = .035$). The assumption of sphericity was violated for the drug x session interaction ($\chi^2(9) = 17.933$, $p = .037$, $\varepsilon = .859$). The interaction between drug and session was not significant ($F(3.434, 68.683) = 0.115$, $p = .965$, $\eta_p^2 = .006$). Figure 116 illustrates the relationship among group, drug, and session.

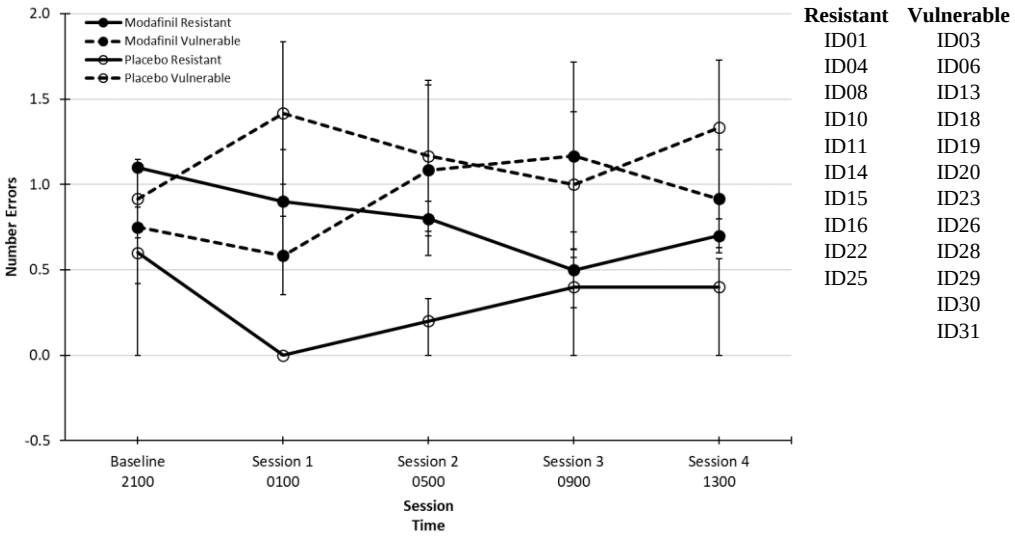


Figure 116. WCST PE: Group by Drug by Session Interaction ($M \pm SE$)

The main effect for group was significant ($F(1, 20) = 4.709$, $p = .042$, $\eta_p^2 = .191$), with performance for the fatigue-resistant group better than performance for the fatigue-vulnerable group. The means (*SE*) for the resistant and vulnerable groups were 0.560 (0.161) and 1.033 (0.147), respectively.

The main effect for drug was not significant ($F(1, 20) = 0.317$, $p = .579$, $\eta_p^2 = .016$. The means (*SE*) for the modafinil and placebo conditions were 0.850 (0.162) and 0.743 (0.125), respectively.

There was not a significant main effect for session ($F(4, 80) = 0.094$, $p = .984$, $\eta_p^2 = .005$). Performance remained relatively stable over the continuous wakefulness period.

FMS: The grouping resulted in 10 individuals in the fatigue-resistant group and 12 in the fatigue-vulnerable group. The average (*SD*) hours of sleep obtained the 3 nights before the placebo visit to the lab were 8.46 (0.62) for the fatigue-resistant group and 8.13 (0.37) for the fatigue-vulnerable group ($t(20) = 1.573$, $p = .131$).

There was not a significant group by drug by session interaction ($F(4, 80) = 0.957$, $p = .436$, $\eta_p^2 = .046$), a significant group by drug interaction ($F(1, 20) = 0.197$, $p = .662$, $\eta_p^2 = .010$), a significant group by session interaction ($F(4, 80) = 0.614$, $p = .654$, $\eta_p^2 = .030$), nor a significant drug by session interaction ($F(4, 80) = 0.388$, $p = .816$, $\eta_p^2 = .019$). Figure 117 illustrates the relationship among group, drug, and session.

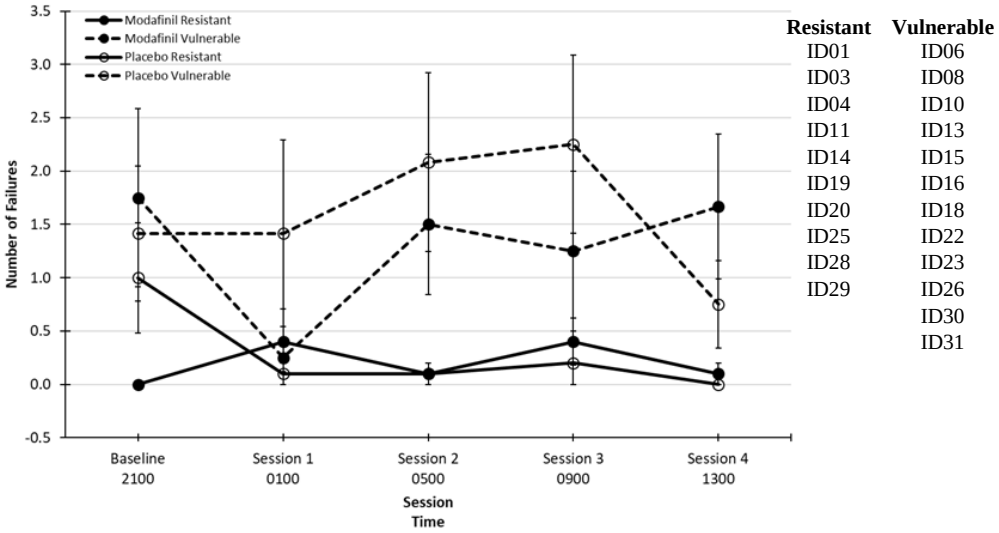


Figure 117. WCST FMS: Group by Drug by Session Interaction ($M \pm SE$)

The main effect for group was significant ($F(1, 20) = 58.169$, $p < .001$, $\eta_p^2 = .744$), with performance for the fatigue-resistant group better than performance for the fatigue-vulnerable group. The means (*SE*) for the resistant and vulnerable groups were 0.240 (0.116) and 1.433 (0.105), respectively.

The main effect for drug was not significant ($F(1, 20) = 0.588$, $p = .452$, $\eta_p^2 = .029$. The means (*SE*) for the modafinil and placebo conditions were 0.742 (0.142) and 0.932 (0.151), respectively.

There was not a significant main effect for session ($F(4, 80) = 0.771$, $p = .548$, $\eta_p^2 = .037$). Although performance fluctuated across the testing period, no sessions were significantly different from any others.

3.2.1.6 Oculometric assessments.

Due to technical issues with the PMI FIT, 9 participants did not have complete oculometric data, leaving a total sample size of 13. The analyses for the oculometric assessments included metrics for constriction latency and saccadic velocity.

Constriction latency: The grouping resulted in 6 individuals in the fatigue-resistant group and 7 in the fatigue-vulnerable group. The average (*SD*) hours of sleep obtained the 3 nights before the placebo visit to the lab were 8.36 (0.66) for the fatigue-resistant group and 8.38 (0.55) for the fatigue-vulnerable group ($t(11) = -0.059$, $p = .954$).

There was not a significant group by drug by session interaction ($F(4, 44) = 0.563$, $p = .691$, $\eta_p^2 = .049$), a significant group by drug interaction ($F(1, 11) = 1.103$, $p = .316$, $\eta_p^2 = .091$), a significant group by session interaction ($F(4, 44) = 1.225$, $p = .314$, $\eta_p^2 = .100$), nor a significant drug by session interaction ($F(4, 44) = 0.315$, $p = .866$, $\eta_p^2 = .028$). Figure 118 shows the pattern of responses among group, drug, and session.

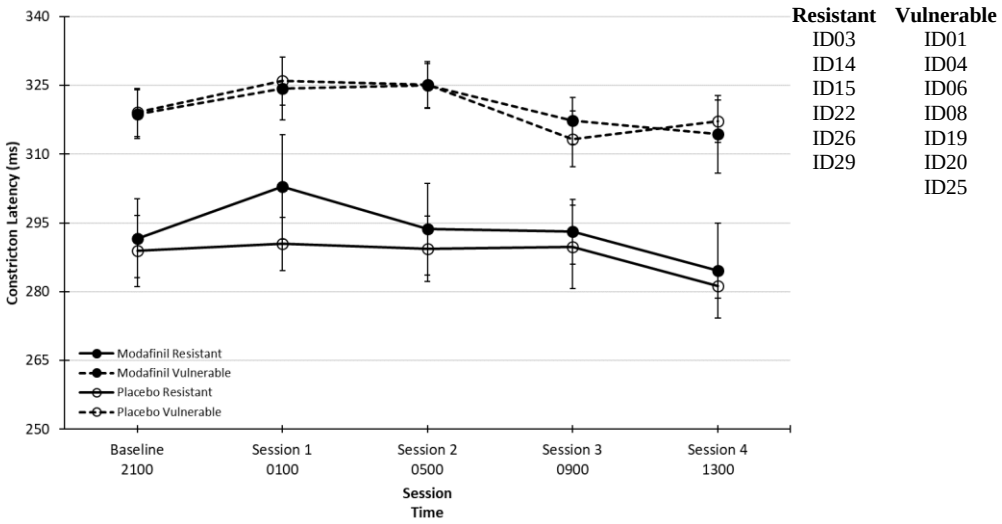


Figure 118. Oculometric PMI Constriction Latency: Group by Drug by Session Interaction (*M* ± *SE*)

The main effect for group was significant ($F(1, 11) = 12.263$, $p = .005$, $\eta_p^2 = .527$), with performance for the fatigue-resistant group better than performance for the fatigue-vulnerable group. The means (*SE*) for the resistant and vulnerable groups were 290.541 (6.173) and 320.002 (5.715), respectively.

The main effect for drug was not significant ($F(1, 11) = 0.937$, $p = .354$, $\eta_p^2 = .079$. The means (*SE*) for the modafinil and placebo conditions were 306.527 (5.092) and 304.017 (3.580), respectively.

There was a significant main effect for session ($F(4, 44) = 6.414$, $p < .001$, $\eta_p^2 = .368$). Post hoc comparisons indicated the baseline session was significantly faster than session 1; session 1 was

significantly slower than sessions 3 and 4; and session 2 was significantly slower than session 4. This effect is shown in Figure 119.

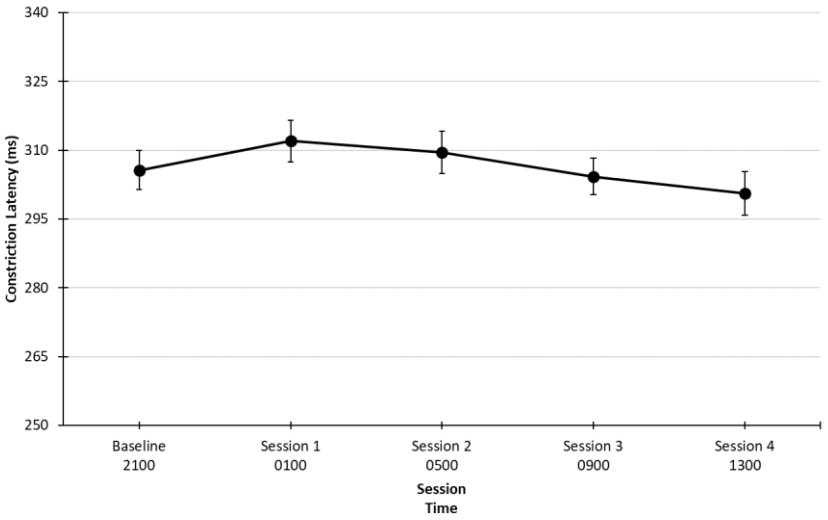


Figure 119. Ocular PMI Constriction Latency: Session Main Effect (*M* ± *SE*)

Saccadic velocity: The grouping resulted in 6 individuals in the fatigue-resistant group and 7 in the fatigue-vulnerable group. The average (*SD*) hours of sleep obtained the 3 nights before the placebo visit to the lab were 8.33 (0.39) for the fatigue-resistant group and 8.40 (0.74) for the fatigue-vulnerable group ($t(11) = -0.212$, $p = .836$).

There was not a significant group by drug by session interaction ($F(4, 44) = 0.382$, $p = .820$, $\eta_p^2 = .034$), a significant group by drug interaction ($F(1, 11) = 0.061$, $p = .810$, $\eta_p^2 = .005$), a significant group by session interaction ($F(4, 44) = 0.167$, $p = .954$, $\eta_p^2 = .015$), nor a significant drug by session interaction ($F(4, 44) = 2.165$, $p = .089$, $\eta_p^2 = .164$). Figure 120 illustrates the pattern of responses among group, drug, and session.

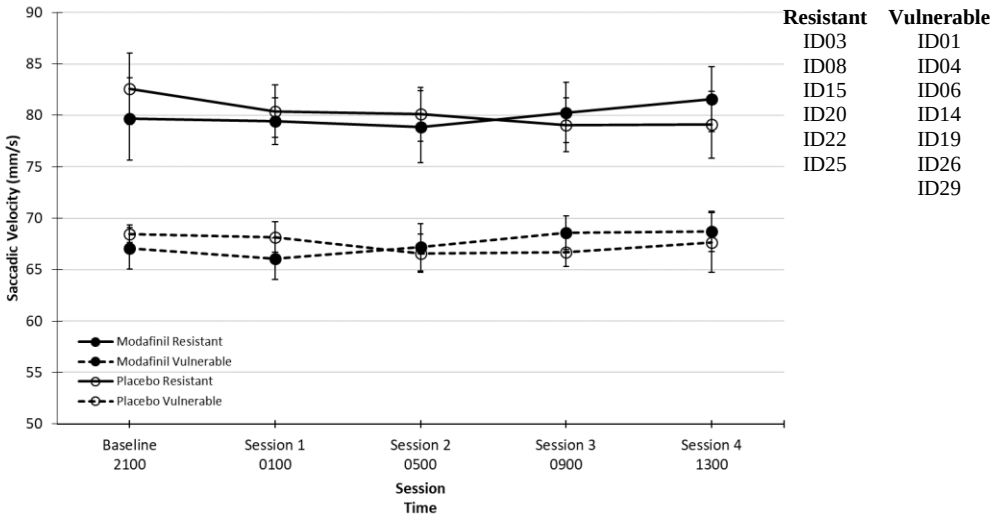


Figure 120. Oculometric PMI Saccadic Velocity: Group by Drug by Session Interaction (*M* ± *SE*)

The main effect for group was significant ($F(1, 11) = 16.779$, $p = .002$, $\eta_p^2 = .604$), with performance for the fatigue-resistant group better than performance for the fatigue-vulnerable group. The means (*SE*) for the resistant and vulnerable groups were 80.107 (2.255) and 67.519 (2.088), respectively.

The main effect for drug was not significant ($F(1, 11) = 0.045$, $p = .837$, $\eta_p^2 = .004$. The means (*SE*) for the modafinil and placebo conditions were 73.747 (1.642) and 73.879 (1.490), respectively.

There was not a significant main effect for session ($F(4, 44) = 0.673$, $p = .614$, $\eta_p^2 = .058$). Saccadic velocity declined during the early morning test, but did not reach statistical significance.

3.2.1.7 Contrast visual acuity

Contrast visual acuity data will be reported by USAARL collaborators elsewhere.

3.2.1.8 Resting electroencephalogram (EEG)

Theta and alpha percent power in the Cz channel were selected to analyze individual differences in the resting electroencephalogram. Eyes-open and eyes-closed data were analyzed separately.

Eyes-Closed Theta: The grouping resulted in 7 individuals in the fatigue-resistant group and 6 individuals in the fatigue-vulnerable group. The average (*SD*) hours of sleep obtained the 3 nights before the placebo visit to the lab were 8.32 (0.65) for the fatigue-resistant group and 8.28 (0.62) for the fatigue-vulnerable group ($t(11) = 0.123$, $p = .904$).

There was not a significant group by drug by and session interaction ($F(4, 44) = 1.895$, $p = .128$, $\eta_p^2 = .147$), a significant group by drug interaction ($F(1,11) = 3.448$, $p = .090$, $\eta_p^2 = .239$), a

significant group by session interaction ($F(1.993, 21.920) = .320$, $p = .729$, $\eta_p^2 = .028$), nor a significant drug by session interaction ($F(4, 44) = 2.406$, $p = .064$, $\eta_p^2 = .179$). The relationship among group, drug, and session is illustrated in Figure 121.

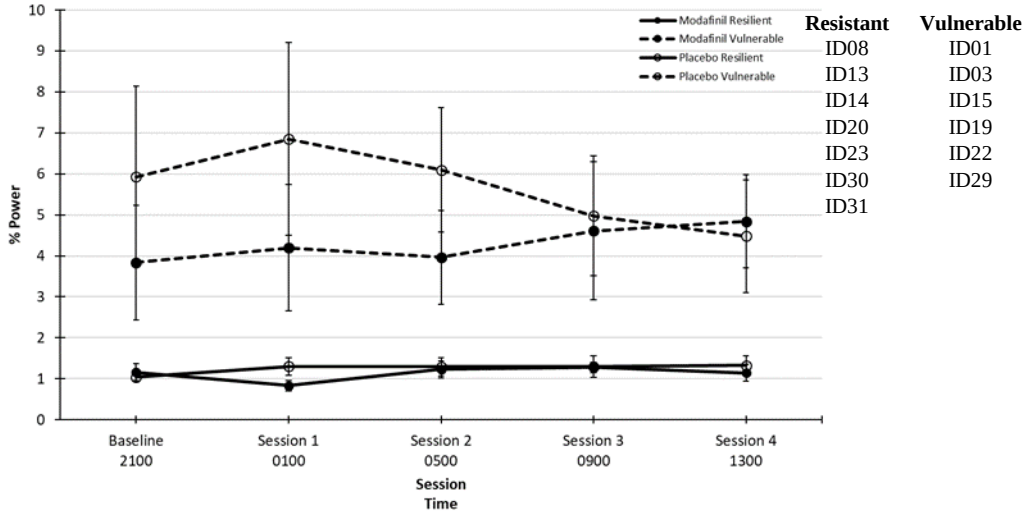


Figure 121. Cz Eyes-Closed Theta: Group by Drug by Session Interaction ($M \pm SE$)

There was a significant main effect of group ($F(1, 11) = 9.847$, $p = .009$, $\eta_p^2 = .472$); percent power was lower in the fatigue-resistant group compared to the fatigue-vulnerable group. The means (*SE*) for the resistant and vulnerable groups were 1.186 (0.959) and 5.614 (1.036), respectively.

There was a significant main effect of drug ($F(1, 11) = 5.535$, $p = .038$, $\eta_p^2 = .335$); percent power was lower during the modafinil condition compared to the placebo condition. The means (*SE*) for the placebo and modafinil conditions were 3.824 (0.850) and 2.976 (0.542), respectively.

The assumption of sphericity was violated for session ($\chi^2(9) = 34.957$, $p < .001$, $\varepsilon = .498$). There was not a main effect for session ($F(1.993, 21.920) = .246$, $p = .783$, $\eta_p^2 = .022$).

Eyes-Open Theta: The grouping resulted in 7 individuals in the fatigue-resistant group and 6 individuals in the fatigue-vulnerable group. The average (*SD*) hours of sleep obtained the 3 nights before the placebo visit to the lab were 8.35 (0.66) for the fatigue-resistant group and 8.25 (0.61) for the fatigue-vulnerable group ($t(11) = 0.269$, $p = .793$).

There was not a significant group by drug by session interaction ($F(4, 44) = 1.585$, $p = .195$, $\eta_p^2 = .126$), a significant group by drug interaction ($F(1,11) = 2.911$, $p = .116$, $\eta_p^2 = .209$), nor a significant group by session interaction ($F(2.899, 31.899) = .518$, $p = .667$, $\eta_p^2 = .045$). The assumption of sphericity was violated for the drug by session interaction ($\chi^2(9) = 30.445$, $p < .001$, $\varepsilon = .715$). The interaction between drug and session was not significant ($F(2.860, 31.462) = 1.405$, $p = .260$, $\eta_p^2 = .113$). The relationship among group, drug, and session is illustrated in Figure 122.

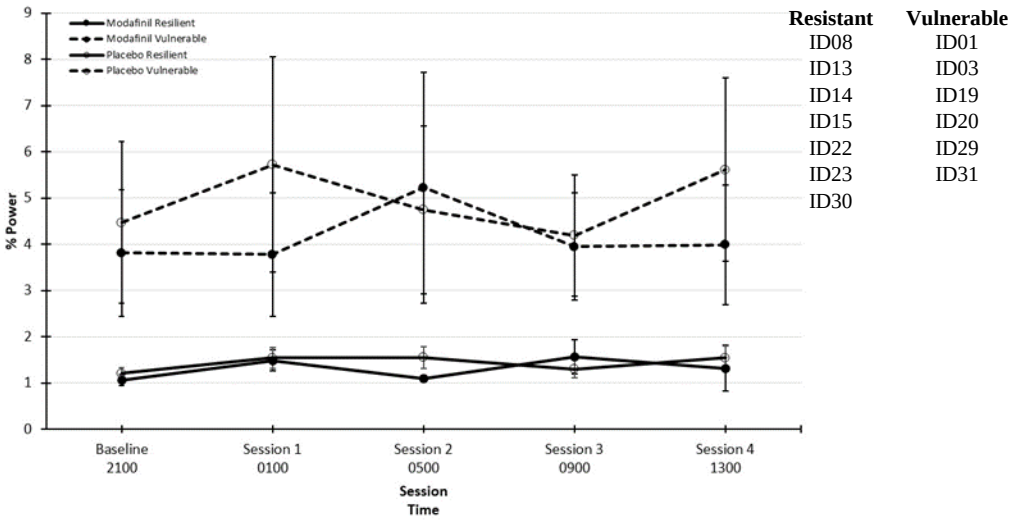


Figure 122. Cz Eyes-Open Theta: Group by Drug by Session Interaction ($M \pm SE$)

There was a significant main effect for group ($F(1, 11) = 5.815$, $p = .035$, $\eta_p^2 = .346$); percent power was lower in the fatigue-resistant group compared to the fatigue-vulnerable group. The means (*SE*) for the resistant and vulnerable groups were 1.277 (1.101) and 5.187 (1.190), respectively.

There was not a significant main effect of drug ($F(1, 11) = 4.720$, $p = .053$, $\eta_p^2 = .300$). The means (*SE*) for the modafinil and placebo conditions were 2.973 (0.727) and 3.491 (0.902), respectively.

The assumption of sphericity was violated for session ($\chi^2(9) = 34.017$, $p < .001$, $\varepsilon = .725$). There was not a main effect of session ($F(2.899, 31.889) = 0.797$, $p = .501$, $\eta_p^2 = .068$).

Eyes-Closed Alpha: The grouping resulted in 6 individuals in the fatigue-resistant group and 7 individuals in the fatigue-vulnerable group. The average (*SD*) hours of sleep obtained the 3 nights before the placebo visit to the lab were 8.49 (0.78) for the fatigue-resistant group and 8.14 (0.42) for the fatigue-vulnerable group ($t(11) = 1.009$, $p = .335$).

There was not a significant group by drug by session interaction ($F(4, 44) = 1.683$, $p = .171$, $\eta_p^2 = .133$), a significant group by session interaction ($F(2.385, 26.234) = 2.489$, $p = .094$, $\eta_p^2 = .185$), a significant group by drug interaction ($F(1,11) = .683$, $p = .426$, $\eta_p^2 = .058$), nor a significant drug by session interaction ($F(2.778, 30.560) = 1.646$, $p = .202$, $\eta_p^2 = .130$). The relationship among group, drug, and session is illustrated in Figure 123.

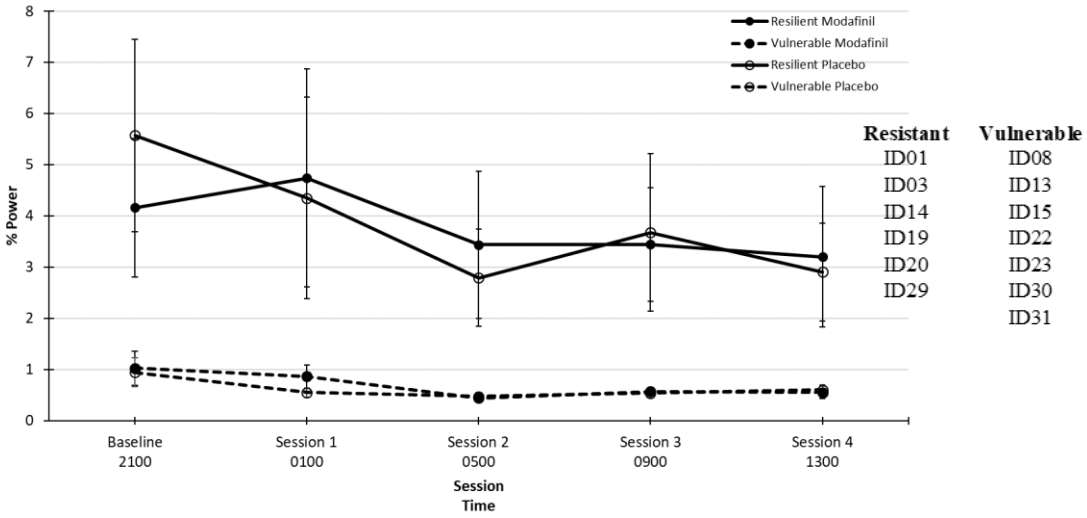


Figure 123. Cz Eyes-Closed Alpha: Group by Drug by Session Interaction ($M \pm SE$)

There was a significant main effect of group ($F(1, 11) = 5.715$, $p = .036$, $\eta_p^2 = .342$) such that power was higher in the fatigue-resistant group. The means (*SE*) for the resistant and vulnerable groups were 3.828 (0.974) and 0.656 (0.901), respectively.

There was not a significant main effect of drug ($F(1, 11) = .002$, $p = .968$, $\eta_p^2 = .000$). The means (*SE*) for the modafinil and placebo conditions were 2.243 (0.672) and 2.240 (0.657), respectively.

The assumption of sphericity was violated for session ($\chi^2(9) = 50.978$, $p < .001$, $\varepsilon = .596$). There was a significant main effect of session ($F(2.385, 26.234) = 6.005$, $p = .005$, $\eta_p^2 = .353$). Post-hoc analyses revealed significant differences between the baseline session and sessions 2 through 4, significant differences between sessions 2 and 3, and significant differences between sessions 3 and 4. This effect is illustrated in Figure 124.

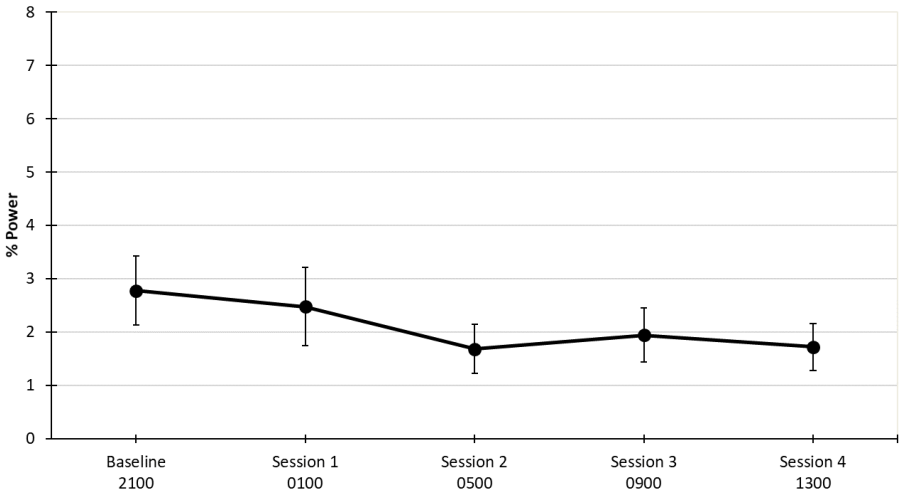


Figure 124. Cz Eyes-Closed Alpha: Session Main Effect (*M* ± *SE*)

Eyes-Open Alpha: The grouping resulted in 6 individuals in the fatigue-resistant group and 7 individuals in the fatigue-vulnerable group. The average (*SD*) hours of sleep obtained the 3 nights before the placebo visit to the lab were 8.49 (0.78) for the fatigue-resistant group and 8.14 (0.42) for the fatigue-vulnerable group ($t(11) = 1.009$, $p = .335$).

There was not a significant group by drug by and session interaction ($F(4, 44) = 2.332$, $p = .071$, $\eta_p^2 = .175$), a significant drug by session interaction ($F(4, 44) = 1.441$, $p = .237$, $\eta_p^2 = .116$), nor a significant group by session interaction ($F(4, 44) = .419$, $p = .794$, $\eta_p^2 = .037$). The relationship among group, drug, and session is illustrated in Figure 125.

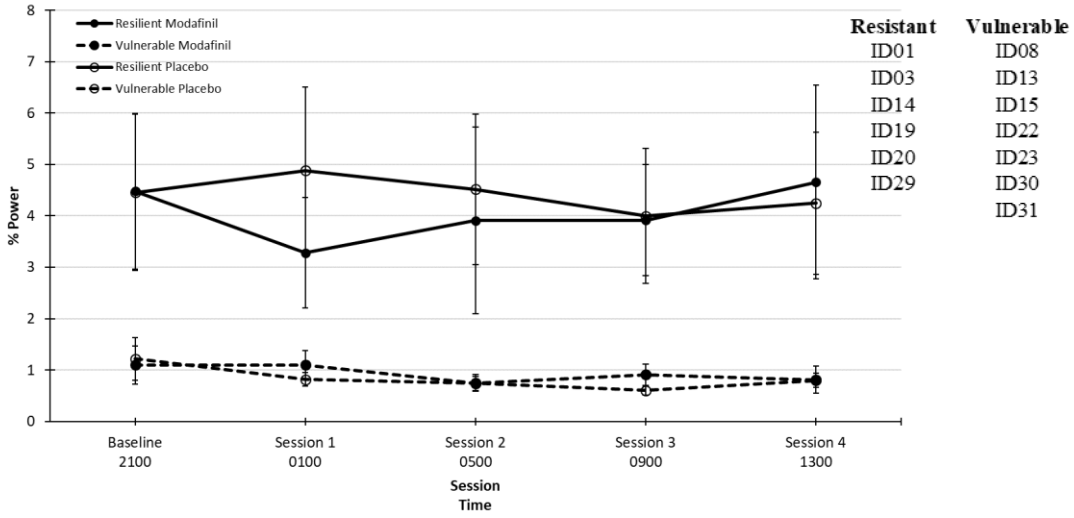


Figure 125. Cz Eyes-Open Alpha: Group by Drug by Session Interaction (*M* ± *SE*)

There was a significant interaction between group and drug ($F(1,11) = 6.245$, $p = .030$, $\eta_p^2 = .362$). Post-hoc analyses revealed significantly lower percent power during the modafinil condition compared to the placebo condition within the fatigue-resistant group; there was no difference between the two drugs in the fatigue-vulnerable group. Within both the modafinil

condition and the placebo condition, there were significant differences between the two groups; percent power was higher in the fatigue-resistant group compared to the fatigue-vulnerable group. This effect is illustrated in Figure 126.

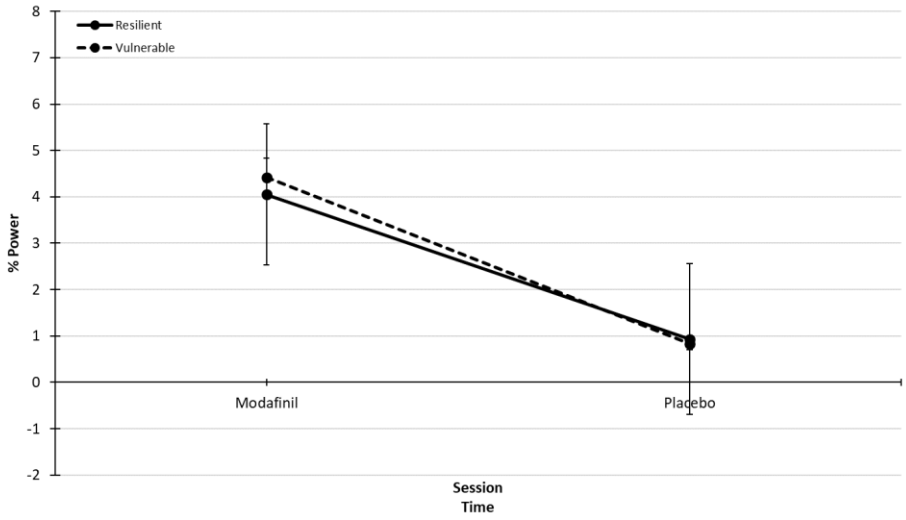


Figure 126. Cz Eyes-Open Alpha: Group by Drug Interaction (*M* ± *SE*)

There was a significant main effect of group ($F(1, 11) = 6.301$, $p = .029$, $\eta_p^2 = .364$) such that power was higher in the fatigue-resistant group. The means (*SE*) for the resistant and vulnerable groups were 4.235 (0.979) and 0.885 (0.907), respectively.

There was not a significant main effect of drug ($F(1, 11) = 2.092$, $p = .176$, $\eta_p^2 = .160$) nor for session ($F(4, 44) = 1.122$, $p = .358$, $\eta_p^2 = .093$). The means (*SE*) for the modafinil and placebo conditions were 2.492 (0.676) and 2.628 (0.662), respectively.

3.2.1.9 Auditory event-related potentials (ERP). The event-related potential analyses for the oddball task included frequency-domain assessment of z-scored alpha power at electrode site Pz near the P3b peak. Data were missing in a session from one participant (placebo, session 1), so the sample mean of the session was included for this session. Thus, no participants were excluded and the total sample size remained at 22. The grouping for this metric resulted in 11 individuals in the fatigue-resistant group and 11 individuals in the fatigue-vulnerable group. Alpha power was analyzed with a three-way ANOVA, with the between-group factor of group (resistant and vulnerable) and repeated measures factors of drug (modafinil and placebo) and session (baseline and sessions 1 through 4). The average (*SD*) hours of sleep obtained the 3 nights before the placebo visit to the lab were 8.37 (0.65) for the fatigue-resistant group and 8.18 (0.32) for the fatigue-vulnerable group ($t(20) = 0.862$, $p = .399$).

The repeated measures ANOVA did not show a significant group by drug by session interaction ($F(4,80) = 1.401$, $p = 0.241$, $\eta_p^2 = 0.065$), a significant group by session interaction ($F(4, 80) = 0.280$, $p = 0.890$, $\eta_p^2 = 0.014$), nor a significant drug by session interaction ($F(4, 80) = 1.975$, $p = 0.106$, $\eta_p^2 = 0.090$). Figure 127 shows the relationship among group, drug, and session.

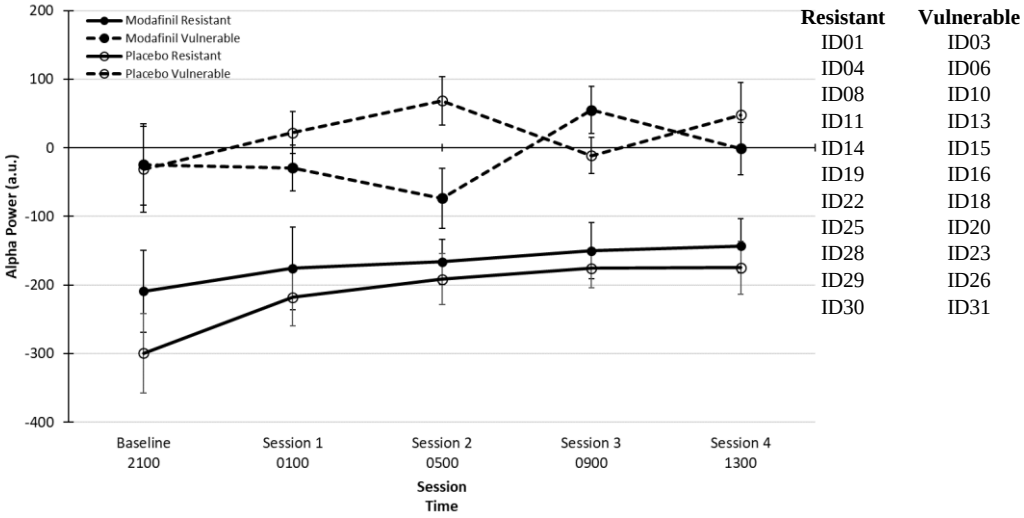


Figure 127. ERP Alpha Power: Group by Drug by Session Interaction ($M \pm SE$)

There was a significant group by drug interaction ($F(1, 20) = 5.335$, $p = 0.032$, $\eta_p^2 = 0.211$). Post hoc analyses revealed significant differences between the two groups after both modafinil and placebo administration. Within each of the groups, there was no difference between the drugs. Results are shown in Figure 128.

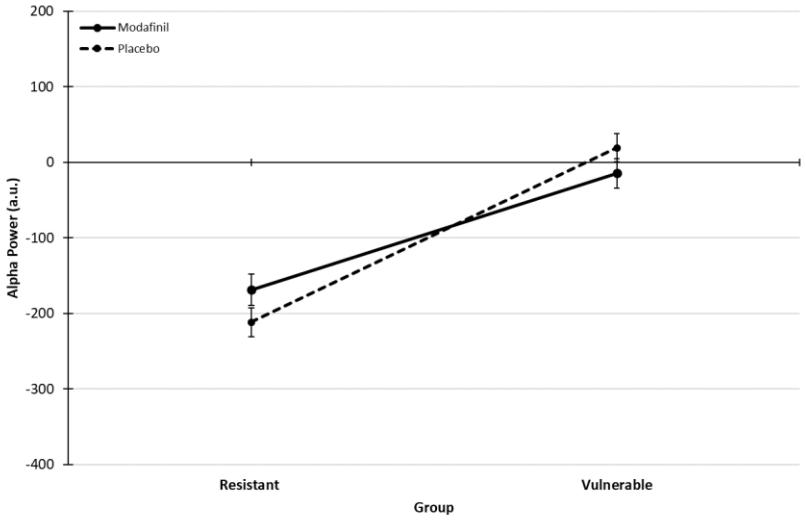


Figure 128. ERP Alpha Power: Group by Drug Interaction ($M \pm SE$)

There was a significant main effect of group ($F(1, 20) = 22.480$, $p < 0.001$, $\eta_p^2 = 0.529$), such that overall alpha suppression was greater (less alert) in the fatigue-resistant group compared with fatigue-vulnerable individuals. The means (*SE*) for the resistant and vulnerable groups were -190.263 (28.713) a.u. and 2.265 (28.713), respectively.

There was no main effect of drug ($F(1, 20) = 0.075$, $p = 0.787$, $\eta_p^2 = 0.004$). The means (*SE*) for the placebo and modafinil conditions were -96.373 (18.200) and -91.726 (25.129) a.u., respectively.

The assumption of sphericity was violated for the main effect of session ($\chi^2(9) = 22.532$, $p = 0.008$, $\varepsilon = 0.779$). The main effect of session was not significant ($F(3.116, 62.324) = 2.499$, $p = 0.066$, $\eta_p^2 = 0.111$).

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

3.2.2.1 POMS. Only two factors from the *POMS* –vigor and fatigue – were analyzed for the individual differences analyses. One person had missing data due to technical issues with the questionnaire program; therefore, 21 participants are included in these analyses.

Vigor: The grouping resulted in 12 individuals in the fatigue-resistant group and 9 in the fatigue-vulnerable group. The average (*SD*) hours of sleep obtained the 3 nights before the placebo visit to the lab were 8.31 (0.55) for the fatigue-resistant group and 8.24 (0.52) for the fatigue-vulnerable group ($t(19) = 0.303$, $p = .765$).

There was not a significant group by drug by session interaction ($F(4, 76) = 0.578$, $p = .680$, $\eta_p^2 = .030$), a significant group by drug interaction ($F(1, 19) = 1.771$, $p = .199$, $\eta_p^2 = .085$), nor a significant group by session interaction ($F(4, 76) = 0.208$, $p = .933$, $\eta_p^2 = .011$). Figure 129 illustrates the relationship among group, drug, and session.

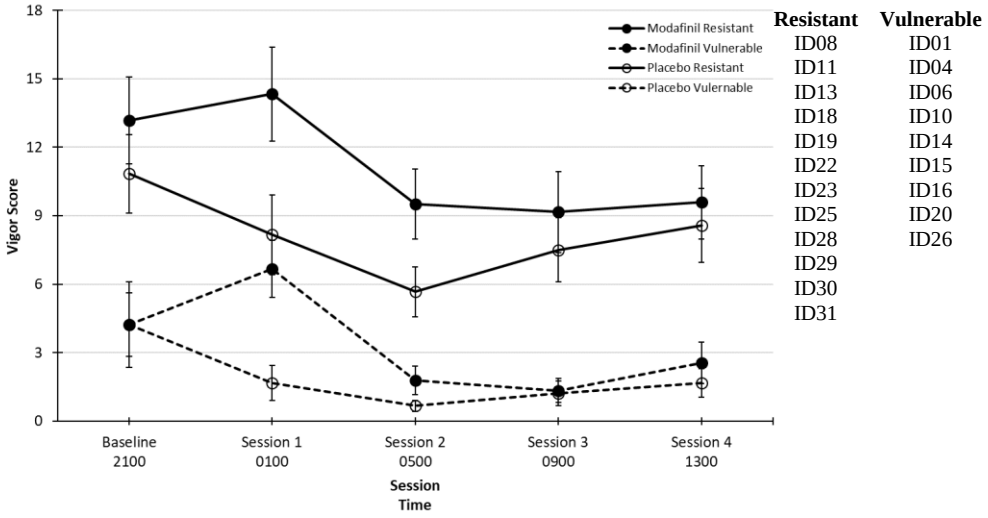


Figure 129. POMS Vigor Score: Group by Drug by Session Interaction (*M* ± *SE*)

The interaction between drug and session was significant ($F(4, 76) = 8.735$, $p < .001$, $\eta_p^2 = .315$). Post hoc analyses indicated differences between the two drugs at sessions 1 and 2, with ratings higher after modafinil administration than after placebo administration. Within the modafinil condition, the baseline session and session 1 ratings of vigor were significantly higher than sessions 2 through 4. Within the placebo condition, the baseline session ratings were significantly higher than sessions 1 through 3; session 1 was significantly higher than session 2; and session 2 was significantly lower than session 4 (marginally lower than session 3, $p = .057$). These effects are illustrated in Figure 130.

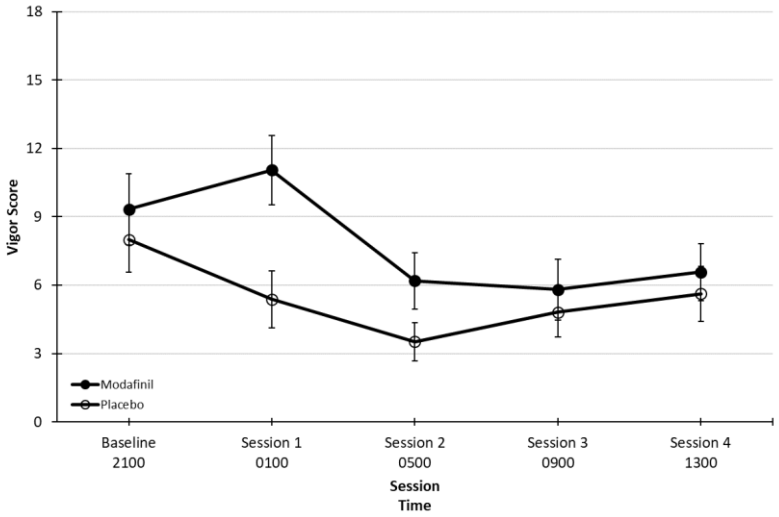


Figure 130. POMS Vigor Score: Drug by Session Interaction ($M \pm SE$)

The main effect for group was significant ($F(1, 19) = 17.771$, $p < .001$, $\eta_p^2 = .483$), with ratings of vigor for the fatigue-resistant group higher than ratings for the fatigue-vulnerable group. The means (*SE*) for the resistant and vulnerable groups were 9.650 (1.095) and 2.600 (1.264), respectively.

The main effect for drug was significant ($F(1, 19) = 13.916$, $p = .001$, $\eta_p^2 = .423$), with ratings of vigor higher for the modafinil condition than for the placebo condition. The means (*SE*) for the modafinil and placebo conditions were 7.231 (0.935) and 5.019 (0.836), respectively.

The assumption of sphericity was violated for the main effect of session ($\chi^2(9) = 18.616$, $p = .029$, $\varepsilon = .798$). There was a significant main effect for session ($F(3.194, 60.682) = 9.424$, $p < .001$, $\eta_p^2 = .332$). Post hoc comparisons indicated that the baseline session and session 1 ratings of vigor were significantly higher than sessions 2 through 4; session 2 was marginally lower than session 4 ($p = .059$). This effect is shown in Figure 131.

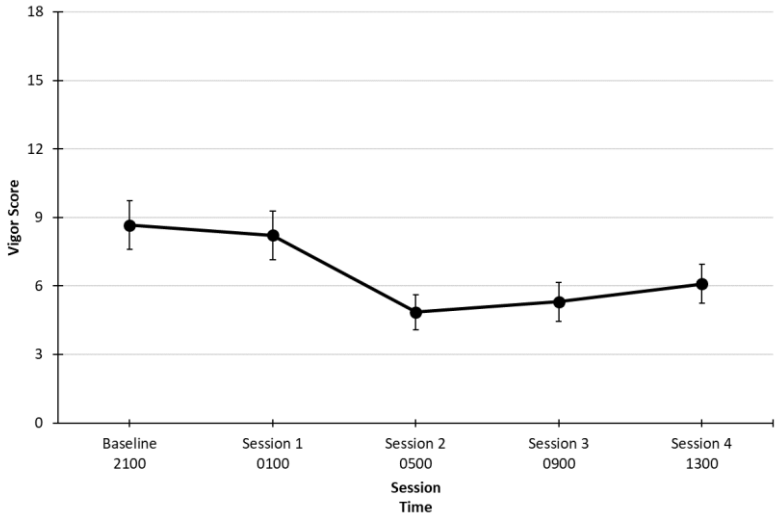


Figure 131. POMS Vigor Score: Session Main Effect (*M* ± *SE*)

Fatigue: The grouping resulted in 10 individuals in the fatigue-resistant group and 11 in the fatigue-vulnerable group. The average (*SD*) hours of sleep obtained the 3 nights before the placebo visit to the lab were 8.50 (0.61) for the fatigue-resistant group and 8.08 (0.35) for the fatigue-vulnerable group ($t(19) = 1.942$, $p = .067$).

There was not a significant group by drug by session interaction ($F(4, 76) = 0.632$, $p = .641$, $\eta_p^2 = .032$) nor a significant group by drug interaction ($F(1, 19) = 0.609$, $p = .445$, $\eta_p^2 = .031$). Figure 132 illustrates the relationship among group, drug, and session.

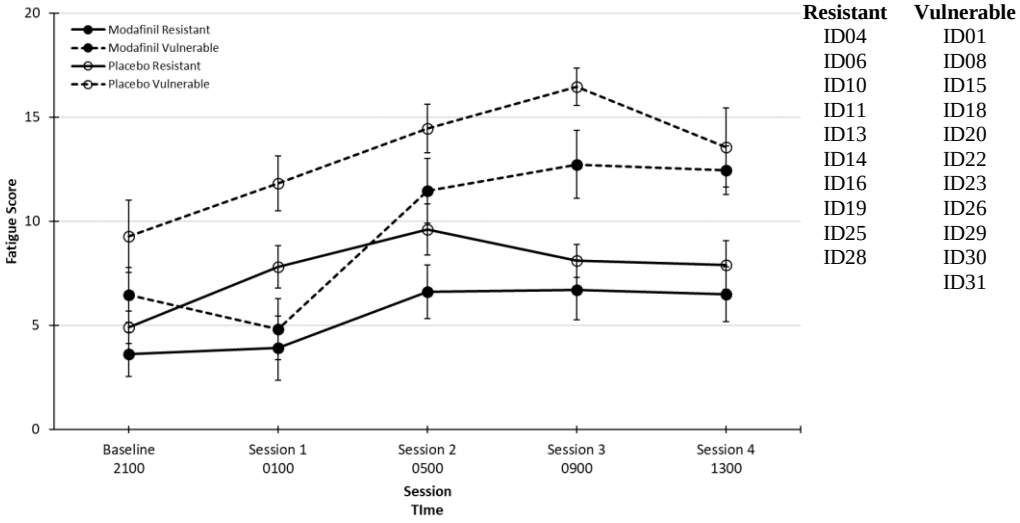


Figure 132. POMS Fatigue Score: Drug by Session Interaction (*M* ± *SE*)

There was a significant group by session interaction ($F(4, 76) = 3.712$, $p = .008$, $\eta_p^2 = .163$). Post hoc analyses indicated differences between the two groups at all sessions, with the fatigue-resistant group outperforming the fatigue-resistant group. Within the fatigue-resistant group, the baseline session and session 1 ratings of fatigue were significantly lower than sessions 2 and 3;

baseline session ratings were marginally lower than session 4 ratings (p = .051). Within the fatigue-vulnerable group, the baseline session and session 1 ratings of fatigue were significantly lower than sessions 2 through 4; session 2 was marginally lower than session 3 (p = .051). These effects are illustrated in Figure 133.

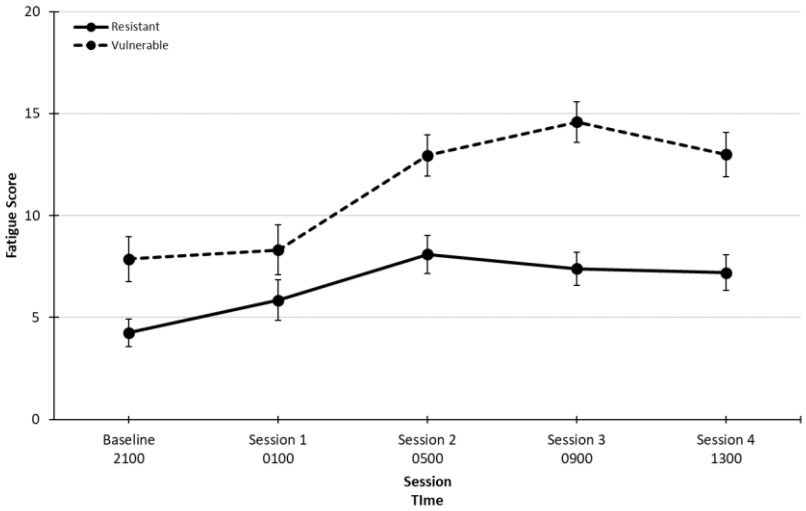


Figure 133. POMS Fatigue Score: Group by Session Interaction ($M \pm SE$)

The assumption of sphericity was violated for the interaction between drug and session ($\chi^2(9)$ = 22.849, p = .007, ε = .752). The interaction between drug and session was significant (F(3.008, 57.144) = 2.952, p = .040, η_p^2 = .134). Post hoc analyses indicated differences between the two drugs at sessions 1 through 3, with ratings of fatigue lower after administration of modafinil compared to after administration of placebo; the drugs were marginally different at the baseline session (p = .059). Within the modafinil condition, the baseline session and session 1 ratings of fatigue were significantly lower than sessions 2 through 4. Within the placebo condition, the baseline session ratings were significantly lower than all sessions; session 1 was significantly lower than sessions 2 and 3. These effects are illustrated in Figure 134.

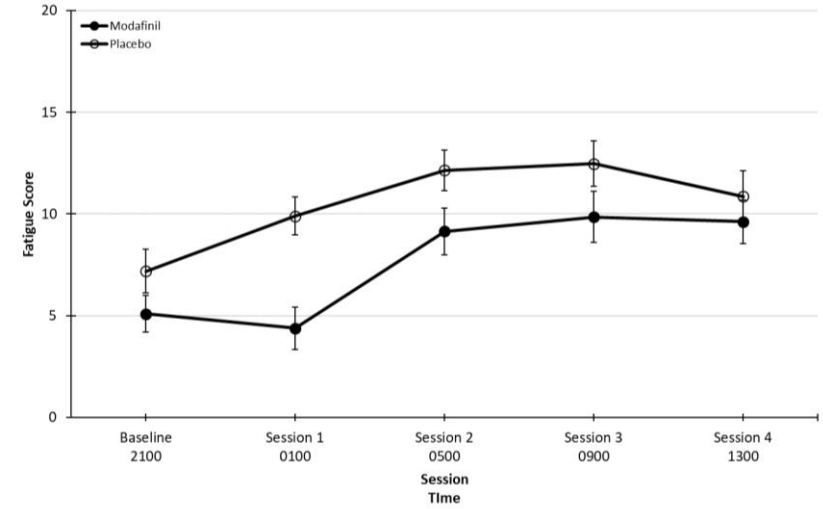


Figure 134. POMS Fatigue Score: Drug by Session Interaction ($M \pm SE$)

The main effect for group was significant ($F(1, 19) = 15.811$, $p = .001$, $\eta_p^2 = .454$), with fatigue ratings for the fatigue-resistant group lower than for the fatigue-vulnerable group. The means (*SE*) for the resistant and vulnerable groups were 6.560 (0.871) and 11.345 (0.830), respectively.

The main effect for drug was significant ($F(1, 19) = 11.341$, $p = .003$, $\eta_p^2 = .374$), with ratings of fatigue lower for the modafinil condition than for the placebo condition. The means (*SE*) for the modafinil and placebo conditions were 7.521 (0.827) and 10.385 (0.634), respectively.

The assumption of sphericity was violated for session ($\chi^2(9) = 20.332$, $p = .016$, $\varepsilon = .812$). There was a significant main effect for session ($F(3.247, 61.691) = 21.728$, $p < .001$, $\eta_p^2 = .533$). Post hoc comparisons indicated that the baseline session and session 1 ratings were significantly lower than all other sessions. This effect is shown in Figure 135.

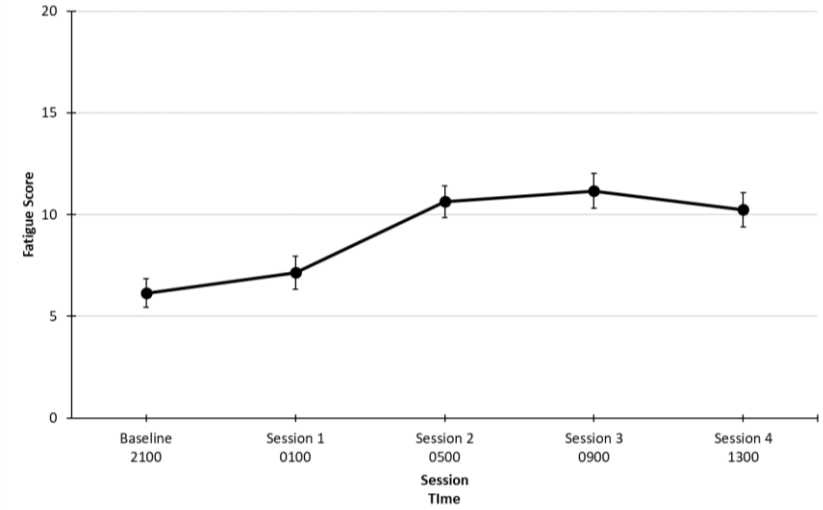
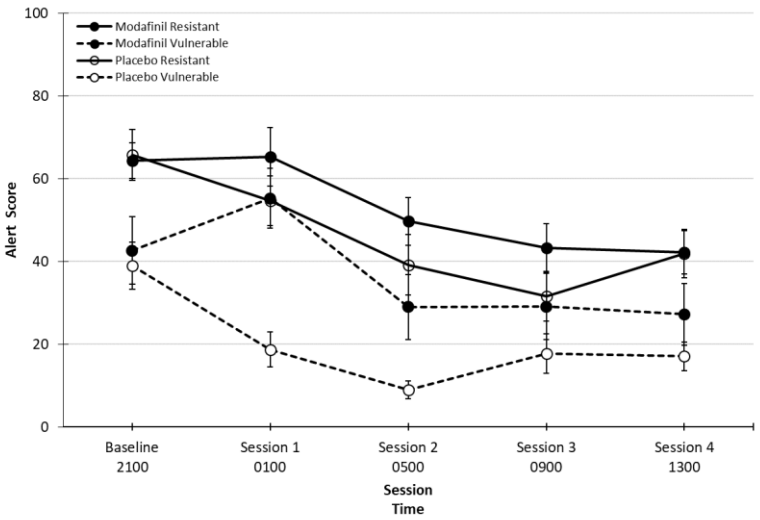


Figure 135. POMS Fatigue Score: Session Main Effect ($M \pm SE$)

3.2.2.2 VAS. Only two factors from the *VAS* – alert/able to concentrate, and sleepiness – were analyzed to determine individual differences in the response to modafinil.

Alert/able to concentrate: The grouping resulted in 12 individuals in the fatigue-resistant group and 10 in the fatigue-vulnerable group. The average (*SD*) hours of sleep obtained the 3 nights before the placebo visit to the lab were 8.13 (0.44) for the fatigue-resistant group and 8.45 (0.56) for the fatigue-vulnerable group ($t(20) = -1.493$, $p = .151$).

There was not a significant group by drug by session interaction ($F(4, 80) = 1.994$, $p = .103$, $\eta_p^2 = .091$), a significant group by drug interaction ($F(1, 20) = 2.364$, $p = .140$, $\eta_p^2 = .106$), nor a significant group by session interaction ($F(4, 80) = 0.782$, $p = .540$, $\eta_p^2 = .038$). Figure 136 illustrates the relationship among group, drug, and session.



Resistant	Vulnerable
ID03	ID01
ID10	ID04
ID13	ID06
ID15	ID08
ID16	ID11
ID18	ID14
ID23	ID19
ID25	ID20
ID28	ID22
ID29	ID26
ID30	
ID31	

Figure 136. VAS Alert Score: Group by Drug by Session Interaction ($M \pm SE$)

The interaction between drug and session was significant ($F(4, 80) = 6.360$, $p < .001$, $\eta_p^2 = .241$). Post hoc analyses indicated differences between the two drugs at sessions 1 through 3, with ratings after modafinil administration higher than after placebo administration. Within the modafinil condition, the baseline session and session 1 ratings of alertness were significantly higher than sessions 2 through 4; the baseline session was marginally lower than session 1 ($p = .053$). Within the placebo condition, the baseline session ratings were significantly higher than sessions 1 through 4; session 1 ratings were significantly higher than sessions 2 and 3. These effects are illustrated in Figure 137.

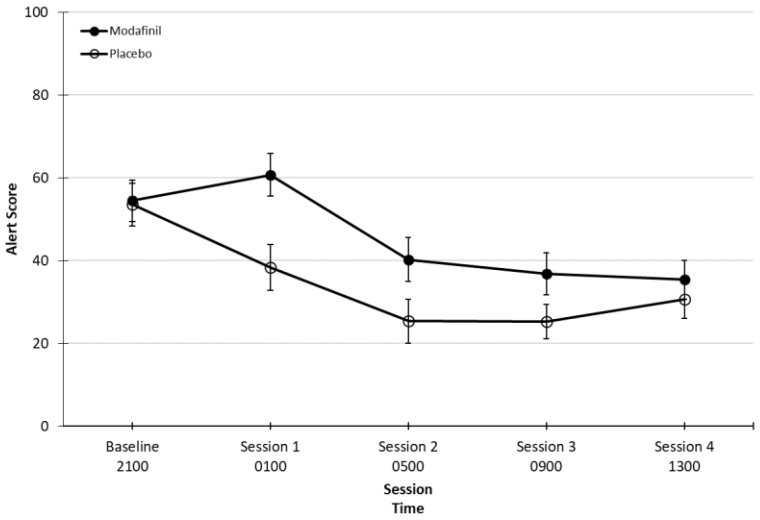


Figure 137. VAS Alert Score: Drug by Session Interaction ($M \pm SE$)

The main effect for group was significant ($F(1, 20) = 13.360$, $p = .002$, $\eta_p^2 = .400$), with alertness ratings for the fatigue-resistant group higher than for the fatigue-vulnerable group. The means (*SE*) for the resistant and vulnerable groups were 49.767 (3.932) and 28.450 (4.307), respectively.

The main effect for drug was significant ($F(1, 20) = 12.374$, $p = .002$, $\eta_p^2 = .382$), with alertness ratings higher for the modafinil than the placebo condition. The means (*SE*) for the modafinil and placebo conditions were 44.793 (3.995) and 33.423 (2.504), respectively.

The assumption of sphericity was violated for session ($\chi^2(9) = 18.751$, $p = .028$, $\varepsilon = .859$). There was a significant main effect for session ($F(3.435, 68.693) = 17.078$, $p < .001$, $\eta_p^2 = .461$). Post hoc comparisons indicated that the baseline session and session 1 ratings of alertness were significantly higher than sessions 2 through 4. This effect is shown in Figure 138.

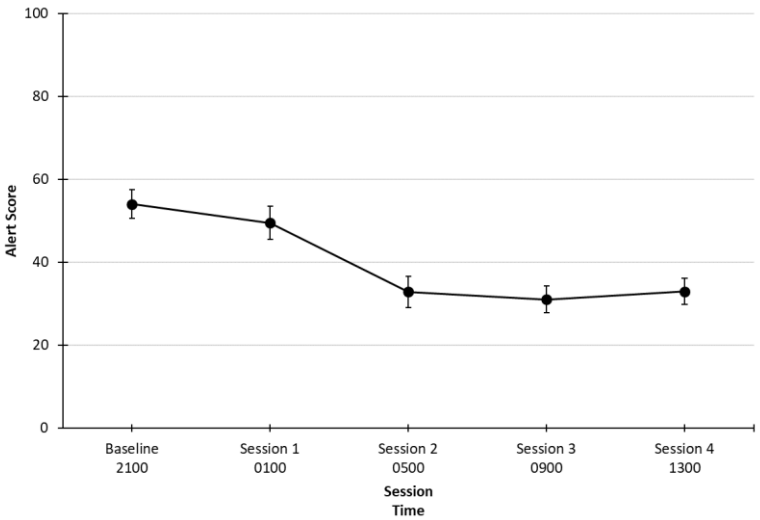


Figure 138. VAS Alert Score: Session Main Effect ($M \pm SE$)

Sleepiness: The grouping resulted in 11 individuals in the fatigue-resistant group and 11 in the fatigue-vulnerable group. The average (*SD*) hours of sleep obtained the 3 nights before the placebo visit to the lab were 8.30 (0.71) for the fatigue-resistant group and 8.25 (0.20) for the fatigue-vulnerable group ($t(11.574) = 0.237$, $p = .817$).

There was not a significant group by drug by session interaction ($F(4, 80) = 0.313$, $p = .868$, $\eta_p^2 = .015$) nor a significant group by session interaction ($F(4, 80) = 0.556$, $p = .695$, $\eta_p^2 = .027$). The group by drug interaction approached statistical significance ($F(1, 20) = 4.110$, $p = .056$, $\eta_p^2 = .170$). Figure 139 illustrates the relationship among group, drug, and session.

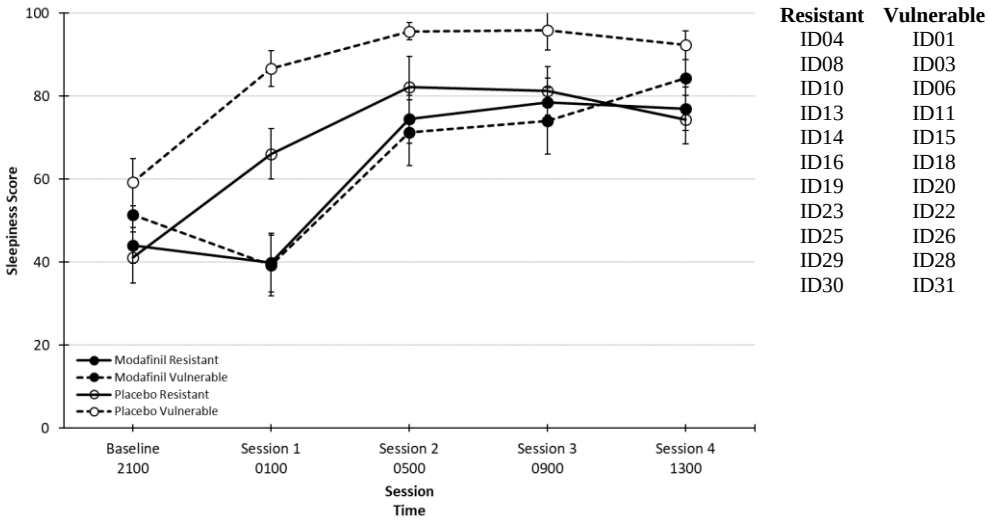


Figure 139. VAS Sleepiness Score: Group by Drug by Session Interaction ($M \pm SE$)

The assumption of sphericity was violated for the interaction between drug and session ($\chi^2(9) = 25.137$, $p = .003$, $\varepsilon = .745$). The interaction between drug and session was significant ($F(2.979, 59.587) = 10.671$, $p < .001$, $\eta_p^2 = .348$). Post hoc analyses indicated differences between the two drugs at sessions 1 through 3, with sleepiness ratings significantly lower after administration of modafinil that compared to that of placebo. Within the modafinil condition, the baseline session and session 1 ratings of sleepiness were significantly lower than sessions 2 through 4; session 2 ratings were significantly lower than session 4. Within the placebo condition, the baseline session ratings were significantly lower than all sessions; session 1 ratings were significantly lower than sessions 2 and 3. These effects are illustrated in Figure 140.

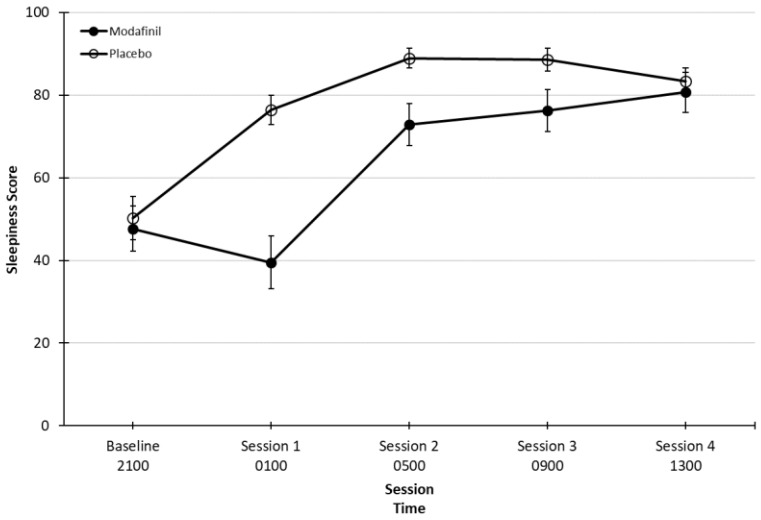


Figure 140. VAS Sleepiness Score: Drug by Session Interaction ($M \pm SE$)

The main effect for group was not significant ($F(1, 20) = 2.919$, $p = .103$, $\eta_p^2 = .127$. The means (SE) for the fatigue-resistant and fatigue-vulnerable groups were 65.864 (3.770) and 74.973 (3.770), respectively.

The main effect for drug was significant ($F(1, 20) = 13.254$, $p = .002$, $\eta_p^2 = .399$) such that sleepiness ratings were higher in the placebo condition. The means (SE) for the modafinil and placebo conditions were 63.382 (4.225) and 77.455 (1.957), respectively.

The assumption of sphericity was violated for session ($\chi^2(9) = 37.121$, $p < .001$, $\varepsilon = .664$). There was a significant main effect for session ($F(2.657, 53.135) = 37.050$, $p < .001$, $\eta_p^2 = .649$). Post hoc comparisons indicated that the baseline session ratings were significantly lower than all other session ratings; session 1 ratings were significantly lower than sessions 2 through 4. This effect is shown in Figure 141.

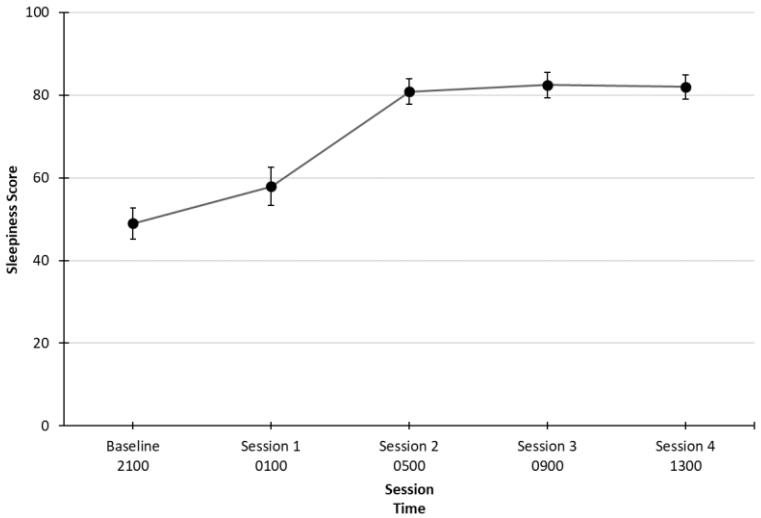


Figure 141. VAS Sleepiness Score: Session Main Effect ($M \pm SE$)

3.3 Discussion

The present study addressed the question of whether modafinil can bring performance levels of individuals susceptible to the effects of sleep deprivation up to levels of those who are more resistant to these effects. Participants were tested over two separate periods of 36 hours of continuous wakefulness, receiving 200mg of modafinil during one period and placebo during the other. Performance from the placebo condition was used to classify participants into fatigue resistant (performance does not notably decline) or fatigue vulnerable (performance markedly declines) groups. Data were compared to determine if modafinil elevated performance of the fatigue-susceptible group to at least the same level as those who were fatigue resistant, as well as determined if the fatigue-resistant group benefited significantly from modafinil.

Results from this study indicated that modafinil attenuated the effects of sleep deprivation on performance, supporting the study hypotheses. Initial analyses indicated that performance on most of the cognitive tasks was positively impacted by modafinil. Lapses and reaction time on the Psychomotor Vigilance Task (PVT) were both improved during the modafinil condition compared to placebo, as were correct responses and reaction times on the all categories of the Stroop task, the Rapid Decision-Making task (RDM), and the Delayed Match to Sample Task (DMTS). The only task which was not impacted by modafinil was the Wisconsin Card-Sorting Task (WCST). Previous research has inconsistent results regarding the effects of sleep deprivation on the WCST (Killgore, 2010), but some have found beneficial effects on this task after modafinil administration (Killgore et al., 2009). A study in which 400mg of modafinil were administered after 44 hours of wakefulness showed improved performance on the WCST. However, the amount of sleep deprivation and the dose of modafinil was greater than in the present study.

Subjective mood was also positively affected by modafinil with increases in vigor scores and decreases in fatigue, anger, and total mood disturbance scores from the Profile of Mood Scale (POMS). The Visual Analogy Scale (VAS) scores also demonstrated increases in alertness and energetic scores and decreases in irritability, jitteriness, and sleepiness scores after the administration of modafinil compared to that of placebo. Brain activity during the resting electroencephalography (EEG) was positively affected by the administration of modafinil. Theta activity was greater during the placebo condition than during the modafinil condition at electrode sites Fz and Cz. Delta activity at site Fz was also greater during the placebo condition than during the modafinil condition, demonstrating higher levels of sleepiness when modafinil was not present.

The individual differences analyses further supported the study hypotheses by revealing that participants were affected differently during sleep deprivation. While performance generally declined over the continuous wakefulness period, some individuals' performance declined more than others. As hypothesized, modafinil benefited those in the fatigue-vulnerable group more so than those in the fatigue-resistant group. After receiving modafinil compared to placebo, those in the fatigue-vulnerable group improved significantly on the number of correct responses and reaction time on the Stroop task, whereas the fatigue-resistant group's performance did not change. In the DMTS task, the fatigue-resistant group showed stable performance throughout the

testing period, regardless of whether they received modafinil or not; however, the fatigue-vulnerable group significantly improved after receiving modafinil compared to their performance after receiving placebo. There were fewer lapses on the PVT in the fatigue-vulnerable group after modafinil than after placebo; modafinil also benefited performance in the fatigue-resistant group, but not to the extent as in the vulnerable group. However, performance was not affected differently by administration of modafinil for either group on the RDM task or the WCST.

In addition to cognitive performance, self-reported fatigue was greater in the fatigue-vulnerable group compared to the fatigue-resistant group, regardless of the drug administered. The subjective experience with modafinil indicates that most people do not "feel" the alerting effects of this alertness aid, which differs from other substances used to decrease sleepiness such as caffeine. Whereas stimulants have both cognitive and physiological effects, modafinil does not have the physiological effects (e.g., high heart rate) which generally are experienced with stimulants. The lack of significant drug effects between the fatigue-resistant and fatigue-vulnerable groups in this study could be attributed to the absence of physiological effects from modafinil. The lack of a subjective impact of modafinil has been noted in other studies as well (Wesensten, Belenky, Kautz, Thorne, & Balkin, 2002).

EEG activity was altered based on whether modafinil or placebo were administered prior to the sleep deprivation period; delta and theta activity were higher at the Cz site following placebo administration compared to modafinil administration, indicating high levels of sleepiness. However, modafinil did not tend to benefit fatigue-vulnerable or fatigue-resistant individuals when brain activity was used to classify individuals into fatigue groups. Only one measure, alpha activity during 2 minutes of eyes-open resting activity, showed differences in response to modafinil based on group assignment; fatigue-resistant individuals showed less alpha activity after modafinil administration than after that of placebo. The sample size was small for these measures, potentially leading to low power for this analysis.

While the fatigue-resistant group generally did not benefit from administration of modafinil, classification into fatigue-response group depended on the task performed. Research into individual differences in response to sleep deprivation has shown that people respond differently based on the task performed (Sprecher et al., 2019; Van Dongen, et al., 2004). This study's data support these previous findings; very few individuals remained in either the fatigue-resistant or fatigue-vulnerable group across all tasks. This is illustrated in Appendix C where each individual's modafinil and placebo scores are plotted by task with better performers (fatigue-resistant individuals) starting at the origin. Note that individuals are ranked differently depending on the task, as well as the metric within each task.

Identification of fatigue vulnerability is important in many sectors of society where inadequate sleep is common, but when work must continue in fields such as in military and emergency operations. However, a reliable measure to identify those individuals who are particularly vulnerable to the effects of sleep deprivation is still not available despite efforts to do so. The PVT, which is the "gold standard" for assessing performance deficits associated with sleep deprivation (Abe, Mollicone, Basner, & Dinges, 2014), has often been suggested as a real-world measure of fatigue vulnerability. However, it should be kept in mind that while this test is highly sensitive to the effects of sleep loss, it may not capture instances of fatigue vulnerability across

all cognitive tasks. Some individuals who perform best on the PVT may not perform the best on higher level cognitive tasks, while those who perform the worst on the PVT may not necessarily perform worse on other cognitive tasks (Frey, Badia, & Wright, 2004). The present study corroborated these findings. The question of establishing the general level of fatigue vulnerability remains difficult to answer. Nevertheless, once individuals are identified as fatigue-vulnerable or -resistant based on their observed responses to sleep loss, decisions can be made regarding the need for countermeasures to improve performance which would otherwise degrade due to the effects of inadequate sleep. As shown by the present study, those most impacted by sleep loss will likely benefit the most from an alertness-enhancing intervention, but the exact extent of the benefit across a variety of tasks appears uncertain.

Some limitations to the present study should be addressed in future research. The small sample size may have led to non-significant results due to the lack of power and may also have precluded detection of smaller effects. Generally, individuals who have difficulty performing tasks when sleep deprived may not volunteer for a sleep deprivation study; therefore, this study may not have been entirely representative of fatigue-vulnerable people. Thus, those identified as fatigue-vulnerable in this study may actually be mildly fatigue-resistant. A larger, more representative sample may lead to greater differences between fatigue-vulnerable and fatigue-resistant groups and more stable categorization.

On some cognitive tasks, minute differences separated fatigue-vulnerable and fatigue-resistant individuals. Thus, groupings may not have been reflective of differences in performance that would be significant in real-world scenarios. Cognitive tasks sometimes lack ecological validity; performance on these tests may not equate to similar performance on occupationally-relevant tasks. Furthermore, total sleep deprivation is not as common as long-term sleep restriction in real-world operations. Long-term sleep restriction possesses compounding effects on cognitive performance that make sleep restriction more hazardous to mission success than occasional total sleep deprivation. More research is needed to determine if these results apply to performance during sleep restriction. Finally, the sample tested in this study consisted of young men which limits the generalizability of the study. Women were not included in this study because they possess shorter circadian rhythms compared to men. Many of the timing decisions in this study were made with circadian rhythm in mind. This shorter circadian rhythm may equate to meaningful differences in how women would have been affected by modafinil and total sleep deprivation and necessitate similar women-only studies.

4.0 CONCLUSIONS

These results demonstrate that adding modafinil as a fatigue countermeasure can aid fatigue-vulnerable individuals, potentially increasing mission safety and success. The benefits of adding modafinil as a fatigue countermeasure are numerous. For example, fatigue-vulnerable individuals demonstrated marked increases in cognitive performance and general mood. In a real-world scenario, this may equate to increased cognitive and tactical flexibility, leading to better war-time outcomes with fewer fatigue-related accidents and adverse effects which may occur with other fatigue countermeasures.

The minimal improvements in performance of fatigue-resistant individuals highlight the necessity of future studies. Pursuing differentiation of those who benefit most from modafinil, or other fatigue countermeasures, allows for more precise resource allocation and tailoring fatigue-countermeasures programs by need rather than a blanket policy across installations.

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SYMBOLS

η_p^2	Partial eta squared
p	Probability
F	F-test
df	Degrees of freedom
ε	Epsilon

ABBREVIATIONS

CorrRT	Correct reaction time
dB	Decibel
DMST	Delayed Match to Sample Task
EEG	Electroencephalogram
EOG	Electrooculogram
ERP	Event-related potentials
FAA	Federal Aviation Association
FFT	Fast Fourier transformation
FMS	Failure to Maintain Set
Hz	Hertz
IncorrRT	Incorrect reaction time
Incorr	Incorrect
LSD	Least Significant Difference
M	Mean
MEQ	Morningness/Eveningness Questionnaire
Mg	Milligram
mL	Milliliters
Msec	Millisecond
NCorr	Number Correct
NIncorr	Number Incorrect
OH	Ohio
OHRP	Office for Human Research Protections
PE	Perseverative errors
PVT	Psychomotor Vigilance Task
RT	Reaction time
RRT	Reciprocal reaction time
SEQ	Side Effects Questionnaire
SE	Standard error
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
TMD	Total Mood Disturbance
UTC	Universal Technology Corporation
WCST	Wisconsin Card Sorting Task

ACRONYMS

AFMSA/SG9	Air Force Medical Support Agency Office of Medical Modernization
ANOVA	Analysis of variance
CRADA	Cooperative Research and Development Agreement
FAC	Fatigue Assessment and Countermeasures
FIT	Fitness Impairment Tester
NAMRU-D	Naval Medical Research Unit Dayton
NEO-PI-R	Revised NEO Personality Inventory
POMS	Profile of Mood States
USAARL	U.S. Army Aeromedical Research Laboratory
VAS	Visual Analogue Scale

Appendix A. Statistical Summaries of Each Analysis

Initial Analyses

Table A- 1. Psychomotor Vigilance Task

Metric	Effect	*F (df)*	*p*	η_p^2
Lapses	**Drug X Session Interaction**	***F*(29, 522) = 8.510**	**< .001**	**.321**
	Drug Main Effect	***F*(1, 18) = 25.783**	**< .001**	**.589**
	Session Main Effect	***F*(29, 522) = 27.189**	**< .001**	**.602**
RRT	**Drug X Session Interaction**	***F*(29, 522) = 9.152**	**< .001**	**.337**
	Drug Main Effect	***F*(1,18) = 7.355**	**.014**	**.290**
	Session Main Effect	**F(29, 522) = 46.465**	**.001**	**.721**

Table A- 2. Stroop Task

Metric	Effect	*F (df)*	*p*	η_p^2
Congruent NCorr	**Drug X Session Interaction**	***F*(3.115, 62.292) = 6.952**	**< .001**	**.258**
	Drug Main Effect	***F*(1, 20) = 18.708**	**<.001**	**.483**
	Session Main Effect	***F*(2.944, 58.879) = 5.155**	**.003**	**.205**
Congruent CorrRT	**Drug X Session Interaction**	***F*(2.075, 41.501) = 3.597**	**.035**	**.152**
	Drug Main Effect	***F*(1,20) = 11.249**	**.003**	**.360**
	Session Main Effect	**F(2.492, 49.845) = 9.148**	**< .001**	**.314**
Cogruent Incorr	**Drug X Session Interaction**	***F*(4, 80) = 6.009**	**< .001**	**.231**
	Drug Main Effect	***F*(1, 20) = 13.902**	**.001**	**.410**
	Session Main Effect	***F*(4, 80) = 2.535**	**.046**	**.113**
Incongruent NCorr	**Drug X Session Interaction**	***F*(2.609, 52.189) = 4.682**	**.008**	**.190**
	Drug Main Effect	***F*(1, 20) = 12.163**	**.002**	**.378**
	Session Main Effect	***F*(2.670, 53.400) = 6.502**	**.001**	**.245**
Incongruent CorrRT	**Drug X Session Interaction**	***F*(3.377, 67.547) = 6.478**	**< .001**	**.245**
	Drug Main Effect	***F*(1, 20) = 80,087**	**.010**	**.288**
	Session Main Effect	***F*(4, 80) = 9.708**	**< .001**	**.327**
Incongruent Incorr	Drug X Session Interaction	*F*(2.465, 49.306) = 2.857	.056	.125
	Drug Main Effect	***F*(1, 20) = 7.816**	**.011**	**.281**
	Session Main Effect	***F*(2.427, 55.719) = 4.927**	**.005**	**.198**
Neutral NCorr	**Drug X Session Interaction**	***F*(2.936, 58.723) = 4.058**	**.011**	**.169**
	Drug Main Effect	***F*(1, 20) = 8.998**	**.007**	**.310**
	Session Main Effect	***F*(2.487, 49.748) = 6.900**	**.001**	**.256**
Neutral CorrRT	**Drug X Session Interaction**	***F*(3.179, 63.581) =4.865**	**.004**	**.196**
	Drug Main Effect	***F*(1, 20) = 9.448**	**.006**	**.321**
	Session Main Effect	***F*(3.382, 67.640) = 10.459**	**< .001**	**.343**
Neutral Incorr	**Drug X Session Interaction**	***F*(4, 80) = 2.628**	**.040**	**.116**
	Drug Main Effect	*F*(1, 20) = 2.943	.102	.128
	Session Main Effect	***F*(2.626, 52.524) = 5.025**	**.005**	**.201**
Inhibition Index	Drug X Session Interaction	*F*(4, 20) = 2.245	.071	.101
	Drug Main Effect	*F*(1, 20) = 0.058	.813	.003
	Session Main Effect	*F*(4, 80) = 1.410	.238	.066

Table A- 3. Rapid Decision Making Task

Metric	Effect	*F (df)*	*p*	η_p^2
NCorr	Drug X Session Interaction	*F*(1.966, 41.278) = 2.942	.065	.123
	Drug Main Effect	***F*(1, 21) = 13.171**	**.002**	**.385**
	Session Main Effect	***F*(2.222, 46.671) = 6.046**	**.004**	**.224**
CorrRT	**Drug X Session Interaction**	***F*(3.252, 68.296) = 6.014**	**.001**	**.223**
	Drug Main Effect	***F*(1, 21) = 13.171**	**.002**	**.385**
	Session Main Effect	***F*(2.702, 56.743) = 20.072**	**.001**	**.489**

Table A- 4. Delayed Match to Sample Task

Metric	Effect	*F (df)*	*p*	η_p^2
NCorr	**Drug X Session Interaction**	***F*(4, 84) = 7.074**	**< .001**	**.252**
	Drug Main Effect	***F*(1, 21) = 8.980**	**.007**	**.300**
	Session Main Effect	***F*(4, 84) = 10.292**	**< .001**	**.329**
CorrRT	Drug X Session Interaction	*F*(4, 84) = 0.748	.562	. 034
	Drug Main Effect	*F*(1, 21) = 3.818	.064	. 154
	Session Main Effect	***F*(4, 84) = 5.739**	**< .001**	**.215**

Table A- 5. Wisconsin Card Sorting Task

Metric	Effect	*F (df)*	*p*	η_p^2
PE	Drug X Session Interaction	*F*(3.374, 70.856) = 0.142	.949	.007
	Drug Main Effect	*F*(1, 21) = .131	.721	.006
	Session Main Effect	*F*(4, 84) = 0.079	.988	. 004
FMS	Drug X Session Interaction	*F*(4, 84) = 0.303	.875	.014
	Drug Main Effect	*F*(1, 21) = 2.443	.133	.104
	Session Main Effect	*F*(4, 84) = 0.884	.477	.040

Table A- 6. Oculometric Assessments

Metric	Effect	*F (df)*	*p*	η_p^2
Amplitude	Drug X Session Interaction	*F*(4, 48) = 1.126	.355	.086
	Drug Main Effect	*F*(1, 12) = 2.412	.146	.167
	Session Main Effect	*F*(4, 48) = 0.880	.483	.068
Pupil Diameter	Drug X Session Interaction	*F*(4, 48) = 1.157	.342	.088
	Drug Main Effect	*F*(1, 12) = 1.947	.188	.140
	Session Main Effect	F(4, 48) = 0.371	.828	.030
Constriction Latency	Drug X Session Interaction	*F*(4, 48) = 0.302,	.875	.025
	Drug Main Effect	*F*(1, 12) = 0.785	.393	.061
	Session Main Effect	***F*(4, 48) = 6.329**	**< .001**	**.345**
Saccadic Velocity	Drug X Session Interaction	*F*(4, 48) = 2.250	.077	.158
	Drug Main Effect	*F*(1, 12) = 0.040	.844	.003
	Session Main Effect	*F*(4, 48) = 0.713	.587	.056

Table A- 7. EEG Results

Metric	Effect	*F (df)*	*p*	η_p^2
FZ Delta	Drug X Eyes X Session Interaction	*F*(1.962, 21.566) = 1.241	.308	.101
	Drug X Session Interaction	*F*(1.517, 16.684) = 2.207	.149	.167
	Drug X Eyes Interaction	*F*(1, 11) = 1.018	.335	.085
	Session X Eyes Interaction	*F*(1.467, 16.160) = 1.201	.312	.098
	Drug Main Effect	*F*(1, 11) = 3.807	.077	.257
	Eyes Main Effect	***F*(1, 11) = 4.903**	**.049**	**.308**
	Session Main Effect	*F*(2.184, 24.028) = 1.559	.230	.124
FZ Theta	Drug X Eyes X Session Interaction	*F*(3.481, 35.659) = 1.033	. 389	. 079
	Drug X Session Interaction	*F*(3.343, 40.115) = 1.796	.158	.130
	Drug X Eyes Interaction	*F*(1, 12) = .328	.578	.027
	Session X Eyes Interaction	*F*(1.828, 21.938) = 1.265	.299	.095
	Drug Main Effect	***F*(1, 12) = 6.028**	**.030**	**.334**
	Eyes Main Effect	*F*(1, 12) = .336	.573	.027
	Session Main Effect	*F*(2.498, 2.118) = 1.297	.292	.098
FZ Alpha	Drug X Eyes X Session Interaction	*F*(3.079, 33.865) = 1.494	.233	.120
	Drug X Session Interaction	*F*(2.983, 32.809) = 1.128	. 352	. 093
	Drug X Eyes Interaction	***F*(1, 11) = 5.000**	**.047**	**.313**
	Session X Eyes Interaction	*F*(1.758, 19.336) = 3.193	.069	.225
	Drug Main Effect	*F*(1, 11) = 1.062	.325	.088
	Eyes Main Effect	***F*(1, 11) = 5.859**	**.034**	**.348**
	Session Main Effect	***F*(1.831, 20.140) = 7.129**	**.005**	**.393**
FZ Beta	Drug X Eyes X Session Interaction	*F*(2.907, 34.878) = 2.401	.086	.167
	Drug X Session Interaction	*F*(2.258, 27.094) = 0.520	.622	.059
	Drug X Eyes Interaction	***F*(1, 11) = 8.423**	**.014**	**. 434**
	Session X Eyes Interaction	*F*(2.703, 32.436) = 1.408	.259	.042
	Drug Main Effect	*F*(1, 12) = 0.592	.456	.047
	Eyes Main Effect	***F*(1, 12) = 4.942**	**.046**	**.292**
	Session Main Effect	***F*(3.037, 36.440) = 5.675**	**.003**	**.321**

Metric	Effect	*F (df)*	*p*	η_p^2
CZ Delta	Drug X Eyes X Session Interaction	$F(4, 48) = 0.762$	.579	.057
	Drug X Session Interaction	$F(4, 48) = 2.338$	.149	.163
	Drug X Eyes Interaction	$F(1, 12) = 0.788$	.392	.062
	Session X Eyes Interaction	$F(4, 48) = 0.946$	.446	.073
	Drug Main Effect	***F*(1, 12) = 5.146**	**.043**	**.300**
	Eyes Main Effect	$F(1, 12) = 2.231$	.161	**.**157
	Session Main Effect	$F(1.598, 19.174) = 1.328$	.282	.100
CZ Theta	Drug X Eyes X Session Interaction	$F(2.319, 27.833) = 1.354$	.277	.101
	Drug X Session Interaction	$F(3.114, 37.371) = 1.862$	.151	.134
	Drug X Eyes Interaction	$F(1, 12) = 0.803$	.388	.063
	Session X Eyes Interaction	$F(1.420, 17.044) = 0.248$	.708	.134
	Drug Main Effect	***F*(1, 12) = 5.101**	**.043**	**.298**
	Eyes Main Effect	$F(1, 12) = 0.061$	.809	.005
	Session Main Effect	$F(4, 48) = 0.719$	.583	.057
CZ Alpha	Drug X Eyes X Session Interaction	$F(2.907, 34.878) = 2.401$	.086	.167
	Drug X Session Interaction	$F(2.258, 27.094) = 0.520$	.622	.059
	Drug X Eyes Interaction	$F(1, 12) = .942$	.351	.073
	Session X Eyes Interaction	$F(2.703, 32.436) = 1.408$	.259	.042
	Drug Main Effect	$F(1, 12) = 0.592$	.456	.047
	Eyes Main Effect	***F*(1, 12) = 4.942**	**.046**	**.292**
	Session Main Effect	***F*(3.037, 36.440) = 5.675**	**.003**	**.321**
CZ Beta	Drug X Eyes X Session Interaction	$F(2.907, 34.878) = 2.401$	.086	.167
	Drug X Session Interaction	$F(2.258, 27.094) = 0.520$	.622	.059
	Drug X Eyes Interaction	$F(1, 11) = .692$	.423	.059
	Session X Eyes Interaction	$F(2.703, 32.436) = 1.408$	.259	.042
	Drug Main Effect	$F(1, 12) = 0.592$	.456	.047
	Eyes Main Effect	***F*(1, 12) = 4.942**	**.046**	**.292**
	Session Main Effect	***F*(3.037, 36.440) = 5.675**	**.003**	**.321**

Metric	Effect	*F (df)*	*p*	η_p^2
PZ Delta	Drug X Eyes X Session Interaction	*F*(2.195, 26.344) = 0.905	.425	.070
	Drug X Session Interaction	*F*(1.229, 14.744) = 0.727	.435	.057
	Drug X Eyes Interaction	*F*(1, 12) = .534	.479	.043
	Session X Eyes Interaction	*F*(2.414, 28.971) = 1.026	.383	.079
	Drug Main Effect	*F*(1, 12) = .774	.396	.061
	Eyes Main Effect	*F*(1, 12) = .710	.416	.056
	Session Main Effect	*F*(1.150, 13.794) = 0.188	.706	.015
PZ Theta	Drug X Eyes X Session Interaction	*F*(7.088, 39.410) = 1.250	.306	.094
	Drug X Session Interaction	*F*(2.475, 29.697) = 1.172	.331	.089
	Drug X Eyes Interaction	*F*(1, 12) = 0.601	.453	.048
	Session X Eyes Interaction	*F*(1.936, 23.231) = 0.514	.599	.041
	Drug Main Effect	*F*(1, 12) = 3.930	.071	.247
	Eyes Main Effect	*F*(1, 12) = .352	.564	.029
	Session Main Effect	***F*(1.658, 19.895) = 4.034**	**.040**	**.252**
PZ Alpha	Drug X Eyes X Session Interaction	*F*(8.996, 52.738) = 2.047	.164	.146
	Drug X Session Interaction	*F*(7.735, 21.299) = 0.755	.467	.059
	Drug X Eyes Interaction	*F*(1, 12) = 1.263	.283	.095
	Session X Eyes Interaction	*F*(2.703, 32.436) = 1.408	.259	.105
	Drug Main Effect	*F*(1, 12) = 0.055	.819	.005
	Eyes Main Effect	*F*(1, 12) = 0.060	.810	.005
	Session Main Effect	*F*(2.031, 24.375) = 2.218	.130	.156
PZ Beta	Drug X Eyes X Session Interaction	*F*(4, 48) = 1.039	.397	. 080
	Drug X Session Interaction	*F*(2.550, 30.604) = 0.402	.721	.032
	Drug X Eyes Interaction	*F*(1, 12) = .009	.924	.001
	Session X Eyes Interaction	*F*(2.468, 29.621) = .834	.466	.065
	Drug Main Effect	*F*(1, 12) = 0.429	.525	.035
	Eyes Main Effect	***F*(1, 12) = 7.179**	**.020**	**.374**
	Session Main Effect	*F*(4,48) = 1.774	.149	.129
	Drug X Session Interaction	*F*(2.258, 27.094) = 0.520	.622	.059
	Drug X Eyes Interaction	*F*(1, 12) = .942	.351	.073
	Session X Eyes Interaction	*F*(2.703, 32.436) = 1.408	.259	.042
	Drug Main Effect	*F*(1, 12) = 0.592	.456	.047
	Eyes Main Effect	***F*(1, 12) = 4.942**	**.046**	**.292**
	Session Main Effect	***F*(3.037, 36.440) = 5.675**	**.003**	**.321**

Table A- 8. ERP Results

Metric	Effect	*F (df)*	*p*	η_p^2
Alpha Suppression	Drug X Session Interaction	*F*(4,84) = 1.9378	.112	.084
	Drug Main Effect	*F*(1,21) = 0.062	.806	003
	Session Main Effect	*F*(2.919, 61.292) = 2.588	.063	.110

Table A- 9. Vital sign measurements

Metric	Effect	*F (df)*	*p*	η_p^2
Diastolic pressure	Drug X Session Interaction	*F*(4, 84) = 0.351	.842	.016
	Drug Main Effect	***F*(1, 21) = 9.358**	**.006**	**.308**
	Session Main Effect	*F*(4, 84) = 0.852	.497	.039
Systolic pressure	Drug X Session Interaction	*F*(4, 84) = 1.515	.205	.067
	Drug Main Effect	*F*(1, 21) = 3.366	.081	.138
	Session Main Effect	***F*(4, 84) = 5.154**	**.001**	**.197**
Heart rate	Drug X Session Interaction	*F*(4, 84) = 0.537	.709	.025
	Drug Main Effect	***F*(1, 21) = 8.253**	**.009**	**.282**
	Session Main Effect	***F*(4, 84) = 2.691**	**.036**	**.144**
Temperature	Drug X Session Interaction	*F*(4, 84) = 0.703	.592	.032
	Drug Main Effect	*F*(1, 21) = 0.844	.369	.039
	Session Main Effect	***F*(4, 84) = 3.694**	**.008**	**.150**

Table A- 10. Profile of Mood States

Metric	Effect	*F (df)*	*p*	η_p^2
Tension	Drug X Session Interaction	*F*(4, 80) = 0.817	.518	.039
	Drug Main Effect	*F*(1,20) = 0.225	.640	.011
	Session Main Effect	*F*(4, 80) = 1.217	.310	.057
Depression	Drug X Session Interaction	*F*(1.640, 32.807) = 0.579	.533	.028
	Drug Main Effect	*F*(1,20) = 2.832	.108	.124
	Session Main Effect	*F*(2.116, 42.313) = 2.209	.120	.099
Anger	**Drug X Session Interaction**	***F*(2.722, 54.449) = 3.519**	**.024**	**.150**
	Drug Main Effect	*F*(1, 20) = 1.850	.189	.085
	Session Main Effect	*F*(3.146, 62.926) = 0.817	.494	.039
Vigor	**Drug X Session Interaction**	***F*(4, 76) = 8.735**	**< .001**	**.315**
	Drug Main Effect	***F*(1, 19) = 13.916**	**< .001**	**.423**
	Session Main Effect	***F*(3.194, 60.682) = 9.424**	**< .001**	**.332**
Fatigue	**Drug X Session Interaction**	***F*(3.008, 57.144) = 2.952**	**.040**	**.134**
	Drug Main Effect	***F*(1, 19) = 11.341**	**.003**	**.374**
	Session Main Effect	***F*(4, 76) = 21.728**	**< .001**	**.533**
Confusion	Drug X Session Interaction	*F*(4, 80) = 1.444	.227	.067
	Drug Main Effect	*F*(1, 20) = 4.282	.052	.176
	Session Main Effect	***F*(4, 80) = 2.815**	**.031**	**.123**
TMD	**Drug X Session Interaction**	***F*(2.374, 47.474) = 5.036**	**.007**	**.201**
	Drug Main Effect	***F*(1, 20) = 12.499**	**.002**	**.385**
	Session Main Effect	***F*(2.918, 58.358) = 15.039**	**< .001**	**.429**

Table A- 11. Visual Analogue Scale

Metric	Effect	*F (df)*	*p*	η_p^2
Alertness/ Able to Concentrate	**Drug X Session Interaction**	***F*(4, 84) = 5.700**	**< .001**	**.213**
	Drug Main Effect	***F*(1, 20) = 10.803**	**.004**	**.340**
	Session Main Effect	***F*(3.241, 68.058) = 17.749**	**< .001**	**.458**
Anxious	Drug X Session Interaction	*F*(4, 84) = 1.837	.129	.080
	Drug Main Effect	*F*(1, 21) = 0.545	.469	.025
	Session Main Effect	***F*(1.796, 37.712) = 3.774**	**.036**	**.152**
Energetic	**Drug X Session Interaction**	***F*(4, 48) = 4.338**	**.003**	**.171**
	Drug Main Effect	***F*(1, 21) = 15.619**	**.001**	**.427**
	Session Main Effect	***F*(3.224, 67.697) = 13.951**	**< .001**	**.399**
Confident	Drug X Session Interaction	*F*(4, 48) = 1.702	.157	.075
	Drug Main Effect	*F*(1, 21) = 2.346	.141	.100
	Session Main Effect	**F(4, 48) = 3.466**	**.011**	**.142**
Irritable	**Drug X Session Interaction**	***F*(3.551, 74.567) = 3.090**	**.025**	**.128**
	Drug Main Effect	***F*(1, 21) = 7.508**	**.012**	**.263**
	Session Main Effect	*F*(3.505, 73.613) = 2.434	.062	.104
Jittery	**Drug X Session Interaction**	***F*(4, 84) = 1.643**	**.017**	**.073**
	Drug Main Effect	*F*(1, 21) = 0.548	.467	.025
	Session Main Effect	***F*(1.889, 39.661) = 3.547**	**.041**	**.145**
Sleepiness	**Drug X Session Interaction**	***F*(2.850, 59.858) = 11.031**	**< .001**	**.344**
	Drug Main Effect	***F*(1, 21) = 11.545**	**.003**	**.355**
	Session Main Effect	***F*(2.563, 53.826) = 37.850**	**< .001**	**.643**
Talkative	Drug X Session Interaction	*F*(3.431, 72.058) = 1.627	.194	.072
	Drug Main Effect	*F*(1, 21) = 1.083	.310	.049
	Session Main Effect	***F*(4, 84) = 4.541**	**.002**	**.178**

Individual Differences Analyses

Table A- 12. Psychomotor Vigilance Task

Metric	Effect	*F (df)*	*p*	η_p^2
Lapses	Group X Drug X Session Interaction	*F*(4, 68) = 0.442	.778	.025
	Group X Drug Interaction	*F*(1, 17) = 1.287	.272	.070
	Group X Session Interaction	*F*(4, 68) = 1.747	.150	.093
	Drug X Session Interaction	***F*(2.942, 56.697) = 8.735**	**.002**	**.259**
	Group Main Effect	***F*(1, 17) = 10.014**	**.006**	**.371**
	Drug Main Effect	**F(1, 17) = 34.754**	**< .001**	**.672**
	Session Main Effect	***F*(3.455,72.914) = 28.428**	**< .001**	**.626**
RRT	Group X Drug X Session Interaction	*F*(4, 68) = 0.271	.896	.016
	Group X Drug Interaction	*F*(1,17) = 1.138	.301	.063
	Group X Session Interaction	*F*(4, 68) = 0.801	.529	.045
	Drug and Session Interaction	***F*(3.337, 56.735) = 7.747**	**< .001**	**.313**
	Group Main Effect	***F*(1, 17) =12.176,**	**.003**	**.417**
	Drug Main Effect	**F(1, 17) = 15.770**	**.001**	**.481**
	Session Main Effect	***F*(4, 68) = 40.785**	**< .001**	**.706**

Table A- 13. Stroop Task

Metric	Effect	*F (df)*	*p*	η_p^2
Incongruent NCorr	**Group X Drug X Session Interaction**	***F*(4, 76) = 5.486**	**.001**	**.224**
	Group X Drug Interaction	**F(1, 19) = 38.296**	**< .001**	**.668**
	Group X Session Interaction	**F(4, 76) = 9.445**	**< .001**	**.332**
	Drug X Session Interaction	***F*(2.103, 39.950) = 7.300**	**.002**	**.278**
	Group Main Effect	***F*(1,19) = 45.945**	**< .001**	**.707**
	Drug Main Effect	***F*(1,19) = 45.246**	**< .001**	**.704**
	Session Main Effect	***F*(2.001, 38.010) = 11.888**	**< .001**	**.385**
Incongruent CorrRT	Group X Drug X Session Interaction	*F*(4, 76) = 0.641	.635	.033
	Group X Drug Interaction	**F(1, 19) = 7.506**	**.013**	**.283**
	Group X Session Interaction	*F*(4, 76) = 0.579	.679	.030
	Drug and Session Interaction	***F*(3.550, 67.456) = 6.184**	**< .001**	**.246**
	Group Main Effect	**F(1, 19) = 23.344**	**< .001**	**.551**
	Drug Main Effect	***F*(1, 19) = 9.857**	**.005**	**.342**
	Session Main Effect	***F*(4, 76) = 9.276**	**< .001**	**.328**

Table A- 14. Rapid Decision Making Task

Metric	Effect	*F (df)*	*p*	η_p^2
NCorr	Group X Drug X Session Interaction	*F*(4, 68) = 2.887	.106	.125
	Group X Drug Interaction	*F*(1, 17) = 0.235	.633	.012
	Group X Session Interaction	*F*(4, 80) = 2.365	.060	.106
	Drug X Session Interaction	F(2.025, 40.500) = 2.867	.068	.125
	Group Main Effect	***F*(1, 20) = 14.923**	**.001**	**.427**
	Drug Main Effect	***F*(1, 20) = 12.691**	**.002**	.388
	Session Main Effect	***F*(2.295, 45.898) = 6.439**	**.002**	.244
CorrRT	Group X Drug X Session Interaction	*F*(4, 80) = 1.437	.229	.067
	Group X Drug Interaction	*F*(1, 20) = 0.551	.466	.027
	Group X Session Interaction	***F*(4, 80) = 7.362**	**< .001**	**.269**
	Drug and Session Interaction	***F*(3.512, 70.233) = 6.139**	**.001**	**.235**
	Group Main Effect	***F*(1, 20) = 30.729**	**.001**	**.606**
	Drug Main Effect	***F*(1, 20) = 13.754**	**.001**	**.407**
	Session Main Effect	***F*(3.514, 70.282) = 26.153**	**< .001**	**.567**

Table A- 15. Delayed Match to Sample Task

Metric	Effect	*F (df)*	*p*	η_p^2
NCorr	**Group X Drug X Session Interaction**	***F*(4, 80) = 6.149**	**< .001**	**.235**
	Group X Drug Interaction	***F*(1, 20) = 5.771**	**.026**	**.224**
	Group X Session Interaction	***F*(4, 80) = 3.430**	**.012**	**.146**
	Drug X Session Interaction	***F*(3.438, 68.753) = 7.556**	**.001**	**.274**
	Group Main Effect	***F*(1, 20) = 18.832**	**< .001**	**.485**
	Drug Main Effect	***F*(1, 20) = 9.533**	**.006**	**.323**
	Session Main Effect	***F*(4, 80) = 10.367**	**< .001**	**.341**
CorrRT	Group X Drug X Session Interaction	*F*(4, 80) = 0.108	. 979	.005
	Group X Drug Interaction	*F*(1, 20) = 0.037	.850	.002
	Group X Session Interaction	*F*(4, 80) = 2.237	.072	.101
	Drug X Session Interaction	*F*(4, 80) = 0.716	.583	. 035
	Group Main Effect	***F*(1, 20) = 39.117**	**< .001**	**.970**
	Drug Main Effect	*F*(1, 20) = 3.643	.071	. 154
	Session Main Effect	***F*(4, 80) = 6.077**	**< .001**	**.233**

Table A- 16. Wisconsin Card Sorting Task

Metric	Effect	*F (df)*	*p*	η_p^2
PE	Group X Drug X Session Interaction	*F*(4, 80) = 0.790	.535	.038
	Group X Drug Interaction	*F*(1, 20) = 3.888	.063	.163
	Group X Session Interaction	*F*(4, 80) = 2.365	.060	.106
	Drug X Session Interaction	*F*(3.434, 68.683) = 0.115	.965	. .006
	Group Main Effect	***F*(1, 20) = 4.709**	**.042**	**.191**
	Drug Main Effect	*F*(1, 20) = 0.317	.579	.016
	Session Main Effect	*F*(4, 80) = 0.094	.984	. 005
FMS	Group X Drug X Session Interaction	*F*(4, 80) = 0.957	.436	.046
	Group X Drug Interaction	*F*(1, 20) = 0.197	.662	.010
	Group X Session Interaction	*F*(4, 80) = 0.614	.654	.030
	Drug X Session Interaction	*F*(4, 80) = 0.388	.816	.019
	Group Main Effect	***F*(1, 20) = 58.169**	**< .001**	**.744**
	Drug Main Effect	*F*(1, 20) = 0.588	.452	.029
	Session Main Effect	*F*(4, 80) = 0.771	.548	.037

Table A- 17. Oculometric Assessments

Metric	Effect	*F (df)*	*p*	η_p^2
Constriction Latency	Group X Drug X Session Interaction	*F*(4, 44) = 0.563	.691	.049
	Group X Drug Interaction	*F*(1, 11) = 1.103	.316	.091
	Group X Session Interaction	*F*(4, 44) = 1.225	.314	.100
	Drug X Session Interaction	*F*(4, 44) = 0.315,	.866	.028
	Group Main Effect	***F*(1, 11) = 12.263**	**. 005**	**.527**
	Drug Main Effect	*F*(1, 11) = 0.937	.354	.079
	Session Main Effect	***F*(4, 44) = 6.414**	**< .001**	**.368**
Saccadic Velocity	Group X Drug X Session Interaction	*F*(4, 44) = 0.382,	.820	.034
	Group X Drug Interaction	*F*(1, 11) = 0.061	.810	.005
	Group X Session Interaction	*F*(4, 44) = 0.167	.954	.015
	Drug X Session Interaction	*F*(4, 44) = 2.165	.089	.164
	Group Main Effect	***F*(1, 11) = 16.779**	**.002**	**.604**
	Drug Main Effect	*F*(1, 11) = 0.045	.837	.004
	Session Main Effect	*F*(4, 44) = 0.673	.614	.058

Table A- 18. EEG Cz

Metric	Effect	*F (df)*	*p*	η_p^2
Eyes Closed Theta	Drug X Group X Session Interaction	$F(4, 44) = 1.895$	. 128	. 147
	Drug X Group Interaction	$F(1,11) = 3.448$	.090	.239
	Session X Group Interaction	$F(1.993, 21.920) = .320$	.729	.028
	Drug X Session Interaction	$F(4, 44) = 2.406$	.064	.179
	Group Main Effect	$\mathbf{F(1, 11) = 9.847}$	**.009**	**.472**
	Drug Main Effect	$\mathbf{F(1, 11) = 5.535}$	**.038**	**.335**
	Session Main Effect	$F(1.993, 21.920) = .246$	.783	.022
Eyes Open Theta	Drug X Group X Session Interaction	$F(2.860, 31.462) = 1.585$	.214	.126
	Drug X Group Interaction	$F(1,11) = 2.911$	.116	.209
	Session X Group Interaction	$F(2.899, 31.899) = .518$	.667	.045
	Drug X Session Interaction	$F(2.860, 31.462) = 1.405$	.260	.113
	Group Main Effect	$\mathbf{F(1, 11) = 5.815}$	**.035**	**.346**
	Drug Main Effect	$F(1, 11) = 4.720$	.053	.300
	Session Main Effect	$F(2.899, 31.889) = .797$	.501	.068
Eyes Closed Alpha	Drug X Group X Session Interaction	$F(2.778, 30.560) = 1.683$	.194	.133
	Drug X Group Interaction	$F(1,11) = .683$	.426	.058
	Session X Group Interaction	$F(2.385, 26.234) = 2.489$	.094	.185
	Drug X Session Interaction	$F(2.778, 30.560) = 1.646$	.202	.130
	Group Main Effect	$\mathbf{F(1, 11) = 5.715}$	**.036**	**.342**
	Drug Main Effect	$F(1, 11) = .002$	.968	.000
	Session Main Effect	$\mathbf{F(2.385, 26.234) = 6.005}$	**.005**	**.353**
Eyes Open Alpha	Drug X Group X Session Interaction	$F(4, 44) = 2.332$	.071	.175
	Drug X Group Interaction	$\mathbf{F(1,11) = 6.245}$	**.030**	**.362**
	Session X Group Interaction	$F(4, 44) = .419$	.794	.037
	Drug X Session Interaction	$F(4, 44) = 1.441$	.237	.116
	Group Main Effect	$\mathbf{F(1, 11) = 6.301}$	**.029**	**.364**
	Drug Main Effect	$F(1, 11) = 2.092$	.176	.160
	Session Main Effect	$F(4, 44) = 1.122$	.358	.093

Table A- 19. ERP

Metric	Effect	*F (df)*	*p*	η_p^2
ERP Alpha Power	Group X Drug X Session Interaction	$F(4,80) = 1.401$	.241	.065
	Group X Drug Interaction	$\mathbf{F(1, 20) = 5.335}$	**.032**	**.211**
	Group X Session Interaction	$F(4, 80) = 0.280$	.890	.014
	Drug X Seession Interaction	$F(4, 80) = 1.975$	.106	.090
	Group Main Effect	$\mathbf{F(1, 20) = 22.480}$	**< .001**	**.529**
	Drug Main Effect	$F(1, 20) = 0.075$	.787	.004
	Session Main Effect	$F(3.116, 62.324) = 2.499$	.066	.111

Table A- 20. Profile of Mood States

Metric	Effect	*F (df)*	*p*	η_p^2
Vigor	Group X Drug X Session Interaction	$F(4, 76) = 0.578$	.680	.030
	Group X Drug Interaction	$F(1, 19) = 1.771$	.199	.085
	Group X Session Interaction	$F(4, 76) = 0.208$	.208	.933
	Drug X Session Interaction	**$F(4, 76) = 8.735$**	**< .001**	.315
	Group Main Effect	**$F(1, 19) = 17.771$**	**< .001**	.483
	Drug Main Effect	**$F(1, 19) = 13.916$**	**< .001**	.423
	Session Main Effect	**$F(3.194, 60.682) = 9.424$**	**< .001**	.332
Fatigue	Group X Drug X Session Interaction	$F(4, 76) = 0.632$	.641	.032
	Group X Drug Interaction	$F(1, 19) = 0.609$	.445	.031
	Group X Session Interaction	**$F(4, 76) = 3.712$**	**.008**	**.163**
	Drug and Session Interaction	**$F(4, 76) = 2.952$**	**.025**	**.134**
	Group Main Effect	**$F(1, 19) = 11.341$**	**.003**	**.374**
	Drug Main Effect	**$F(1, 19) = 13.916$**	**.001**	**.423**
	Session Main Effect	**$F(3.247, 61.691) = 21.728$**	**< .001**	**.533**

Table A- 21. Visual Analogue Scale

Metric	Effect	*F (df)*	*p*	η_p^2
Alertness/ Able to Concentrate	Group X Drug X Session Interaction	$F(4, 80) = 1.994$	.103	.091
	Group X Drug Interaction	$F(1, 20) = 2.364$	.140	.106
	Group X Session Interaction	$F(4, 80) = 0.782$	.540	.038
	Drug X Session Interaction	**$F(4, 80) = 6.360$**	**< .001**	.241
	Group Main Effect	**$F(1, 20) = 13.360$**	**.002**	**.400**
	Drug Main Effect	**$F(1, 20) = 12.374$**	**.002**	**.382**
	Session Main Effect	**$F(3.435, 68.693) = 17.078$**	**< .001**	**.461**
Sleepiness	Group X Drug X Session Interaction	$F(4, 80) = 0.313$	.868	.015
	Group X Drug Interaction	$F(1, 20) = 4.110$	.056	.170
	Group X Session Interaction	$F(4, 80) = 0.556$	.695	.027
	Drug X Session Interaction	**$F(2.979, 59.587) = 10.671$**	**< .001**	**.348**
	Group Main Effect	$F(1, 20) = 2.919$	.103	.127
	Drug Main Effect	**$F(1, 20) = 13.254$**	**.002**	**.399**
	Session Main Effect	**$F(2.657, 53.135) = 37.050$**	**< .001**	**.649**

Appendix B. Side Effects Questionnaire Responses

	BL		T1		T2		T3		T4	
Trouble staying awake	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	4	7	1	10	1	4	1	2	1	1
Slight	10	10	5	7	0	5	3	8	5	5
Moderate	6	5	10	5	9	9	9	7	10	12
Severe	2	1	6	0	12	4	8	5	5	4

	BL		T1		T2		T3		T4	
Chills	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	18	17	14	18	12	12	14	13	15	14
Slight	4	5	6	4	7	9	5	9	4	8
Moderate	0	0	2	0	2	1	2	0	2	0
Severe	0	0	0	0	1	0	0	0	0	0

	BL		T1		T2		T3		T4	
Loss of Balance	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	22	22	21	22	17	21	20	22	20	21
Slight	0	0	1	0	5	1	1	0	1	1
Moderate	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0

	BL		T1		T2		T3		T4	
Numbness	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	22	22	22	22	20	21	21	22	21	21
Slight	0	0	0	0	0	1	0	0	0	1
Moderate	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0

	BL		T1		T2		T3		T4	
Dry Mouth	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	19	18	17	15	19	17	17	17	16	17
Slight	3	4	5	7	3	3	3	5	4	4
Moderate	0	0	0	0	0	2	1	0	1	1
Severe	0	0	0	0	0	0	0	0	0	0

	BL		T1		T2		T3		T4	
Nervous	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	21	21	20	21	18	19	20	21	18	20
Slight	1	1	2	1	4	3	1	1	3	2
Moderate	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0

	BL		T1		T2		T3		T4	
Anxiety	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	20	19	17	19	18	16	16	17	15	17
Slight	1	2	3	2	2	4	3	4	4	3
Moderate	0	1	1	1	2	2	1	1	1	2
Severe	1	0	1	0	1	0	1	0	1	0

	BL		T1		T2		T3		T4	
Stomach Cramps	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	20	22	18	21	18	18	19	19	18	20
Slight	2	0	4	2	3	4	2	3	3	2
Moderate	0	0	0	0	1	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0

	BL		T1		T2		T3		T4	
Muscle Cramps	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	21	21	20	20	21	18	20	20	20	20
Slight	1	1	2	2	1	3	0	2	1	2
Moderate	0	0	0	0	0	1	1	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0

	BL		T1		T2		T3		T4	
Visual Illusions	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	20	21	18	18	17	16	15	17	14	16
Slight	2	1	4	4	5	6	5	5	5	6
Moderate	0	0	0	0	0	0	1	0	2	0
Severe	0	0	0	0	0	0	0	0	0	0

	BL		T1		T2		T3		T4	
Drugged Feeling	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	21	19	17	19	15	19	15	19	14	18
Slight	1	3	5	3	5	3	5	3	5	4
Moderate	0	0	0	0	2	0	1	1	2	1
Severe	0	0	0	0	0	0	0	0	0	0

	BL		T1		T2		T3		T4	
Lightheaded	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	21	20	22	20	20	21	21	19	20	20
Slight	1	2	0	2	2	1	0	3	1	2
Moderate	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0

	BL		T1		T2		T3		T4	
Difficulty Staying Awake	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	6	8	2	12	2	6	3	4	3	3
Slight	10	9	6	7	1	3	1	7	2	6
Moderate	4	4	8	3	9	10	9	8	11	9
Severe	2	1	6	0	10	3	8	3	5	4

	BL		T1		T2		T3		T4	
Excessive Thirst	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	18	20	21	21	21	17	19	19	19	19
Slight	4	2	1	1	0	5	1	3	1	3
Moderate	0	0	0	0	1	0	1	0	1	0
Severe	0	0	0	0	0	0	0	0	0	0

	BL		T1		T2		T3		T4	
Can't Remember Entire Periods of Time	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	21	22	21	22	19	21	18	21	18	21
Slight	1	0	1	0	3	1	3	1	3	1
Moderate	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0

	BL		T1		T2		T3		T4	
Difficulty Remembering Recent Events	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	21	22	20	21	17	19	17	20	18	20
Slight	1	0	2	1	5	3	4	1	3	2
Moderate	0	0	0	0	0	0	0	1	0	0
Severe	0	0	0	0	0	0	0	0	0	0

	BL		T1		T2		T3		T4	
Irritability	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	19	18	13	18	12	16	12	16	13	17
Slight	4	3	7	3	7	3	6	5	6	3
Moderate	2	1	5	0	4	3	3	1	2	2
Severe	0	0	0	1	0	0	0	0	0	0

	BL		T1		T2		T3		T4	
Loss of Coordination	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	21	19	20	20	17	18	12	19	15	17
Slight	0	3	1	2	3	2	8	2	6	4
Moderate	1	0	1	0	2	2	1	1	0	1
Severe	0	0	0	0	0	0	0	0	0	0

	BL		T1		T2		T3		T4	
Irregular Heartbeat	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	22	22	22	22	22	22	21	22	21	22
Slight	0	0	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0

	BL		T1		T2		T3		T4	
Tremor	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	21	21	22	21	21	21	20	21	21	21
Slight	1	1	0	1	1	0	1	1	0	1
Moderate	0	0	0	0	0	1	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0

	BL		T1		T2		T3		T4	
General Discomfort	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	13	14	10	13	8	10	12	11	10	10
Slight	7	8	7	9	9	9	5	8	9	9
Moderate	2	0	5	0	4	3	4	3	2	3
Severe	0	0	0	0	1	0	0	0	0	0

	BL		T1		T2		T3		T4	
Fatigue	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	3	6	1	10	0	3	0	2	0	1
Slight	11	9	5	6	1	5	5	4	4	5
Moderate	7	5	11	5	13	10	9	11	12	10
Severe	1	0	5	0	8	2	7	1	5	4

	BL		T1		T2		T3		T4	
Boredom	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	8	8	7	10	7	8	8	8	8	6
Slight	11	11	7	8	5	8	2	8	5	8
Moderate	3	3	8	4	8	6	10	5	7	7
Severe	0	0	0	0	2	0	1	1	1	1

	BL		T1		T2		T3		T4	
Drowsiness	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	6	9	6	14	4	5	4	9	6	6
Slight	12	9	3	5	5	6	2	4	4	6
Moderate	3	3	8	2	8	7	10	5	6	6
Severe	1	1	5	1	5	4	5	4	5	4

	BL		T1		T2		T3		T4	
Headache	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	18	18	19	15	17	18	17	20	16	18
Slight	4	4	3	6	4	3	3	2	5	4
Moderate	0	0	0	1	1	1	1	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0

	BL		T1		T2		T3		T4	
Nausea	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	22	22	22	22	21	21	21	20	21	21
Slight	0	0	0	0	1	1	0	2	0	1
Moderate	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0

	BL		T1		T2		T3		T4	
Difficulty Concentrating	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	09	10	3	12	3	6	3	6	5	6
Slight	11	8	7	8	6	5	4	8	7	10
Moderate	2	4	11	2	9	9	10	6	7	5
Severe	0	0	1	0	4	2	4	2	2	1

	BL		T1		T2		T3		T4	
Mental Depression	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	21	22	21	22	21	22	20	21	20	22
Slight	1	0	1	0	0	0	0	1	1	0
Moderate	0	0	0	0	1	0	1	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0

	BL		T1		T2		T3		T4	
Dizziness with Eyes Open	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	22	22	21	21	21	21	20	21	20	21
Slight	0	0	1	1	1	1	1	0	1	1
Moderate	0	0	0	0	0	0	0	1	0	0
Severe	0	0	0	0	0	0	0	0	0	0

	BL		T1		T2		T3		T4	
Vertigo	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	22	22	22	22	22	22	21	22	21	22
Slight	0	0	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0

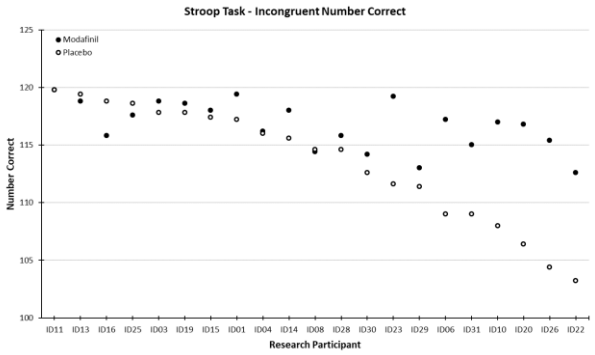
	BL		T1		T2		T3		T4	
Confusion	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	22	22	19	22	18	21	19	22	20	22
Slight	0	0	3	0	4	1	1	0	1	0
Moderate	0	0	0	0	0	0	1	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0

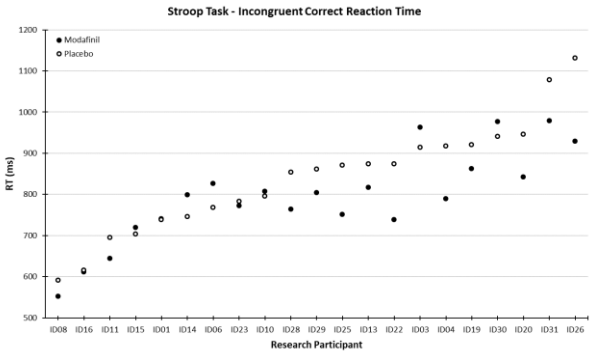
	BL		T1		T2		T3		T4	
Vomiting	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	22	22	22	22	22	22	21	22	21	22
Slight	0	0	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0

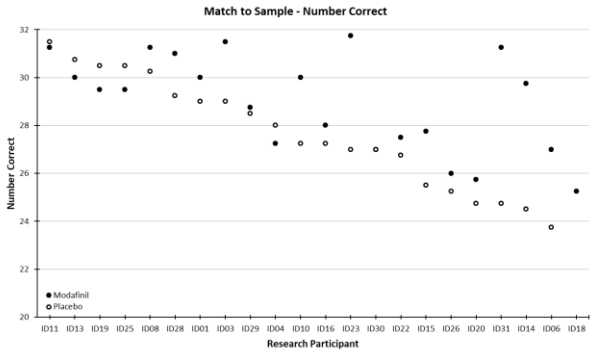
	BL		T1		T2		T3		T4	
Rapid Heart Beats	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil	Placebo*	Modafinil	Placebo*	Modafinil
None	22	22	22	21	22	22	21	22	21	22
Slight	0	0	0	1	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0

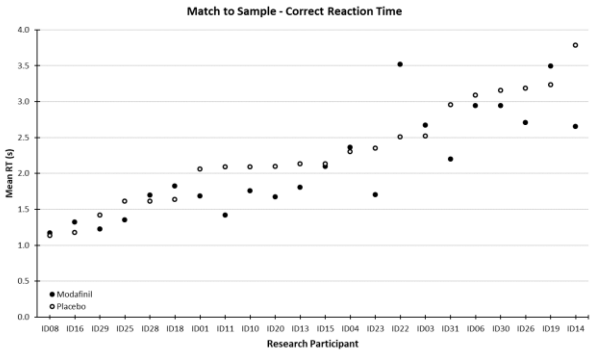
* N=21

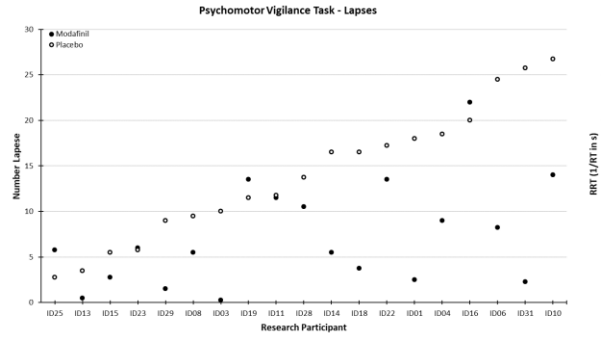
Appendix C. Individual Plots by Drug Condition

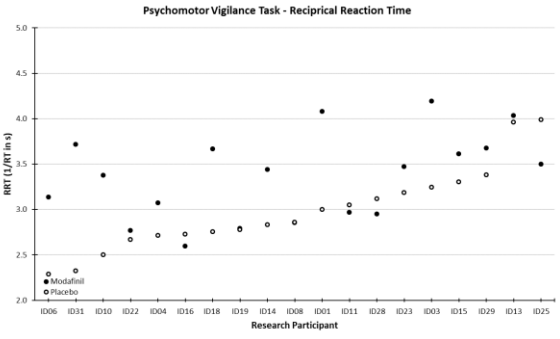


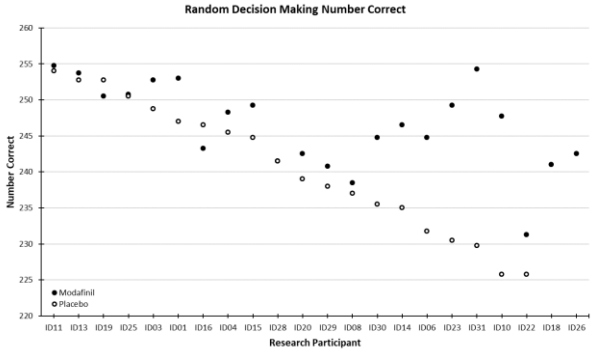


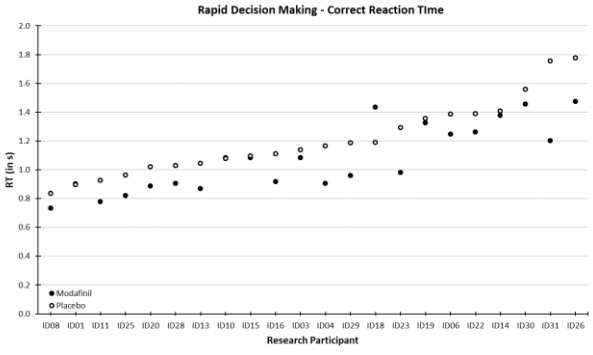


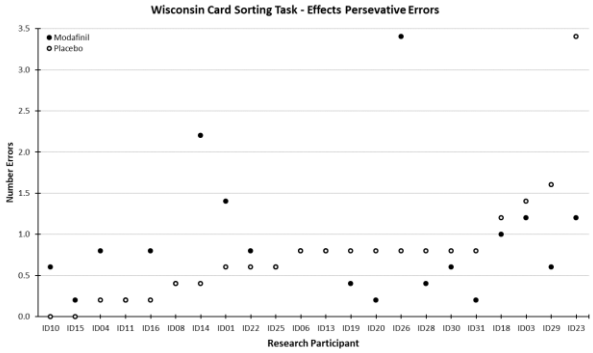


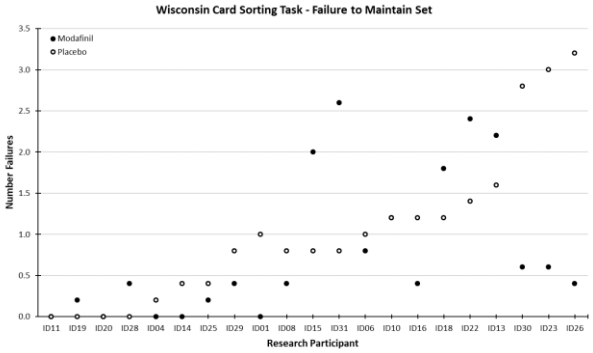


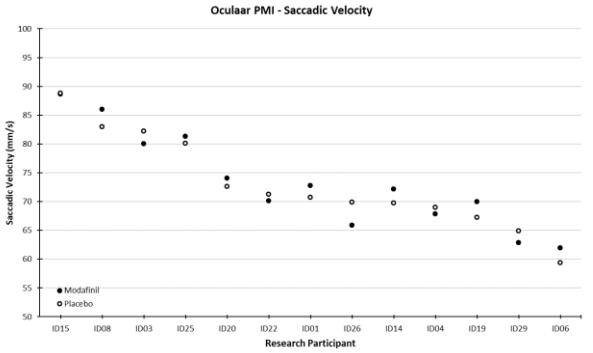


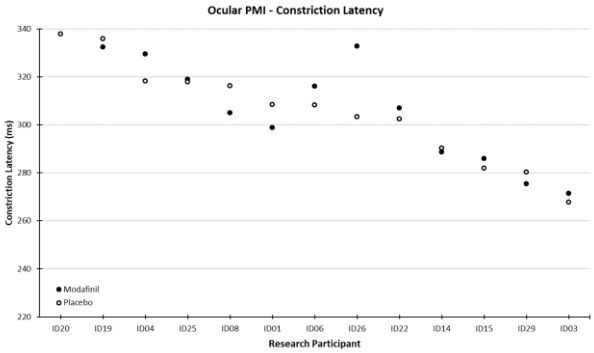


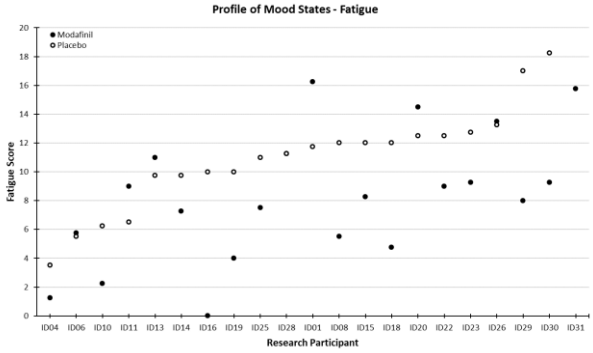


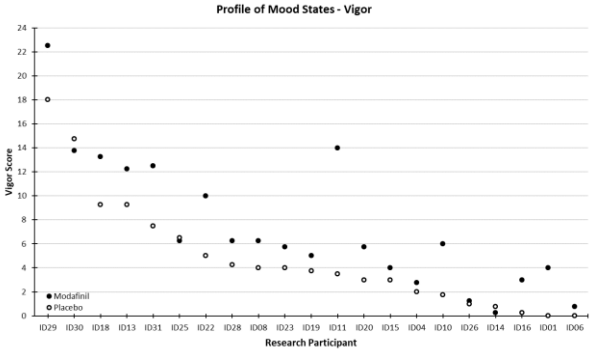

Wisconsin Card Sorting Task - Effects Persevative Errors
Modafinil
Placebo
Number Errors
Research Participant

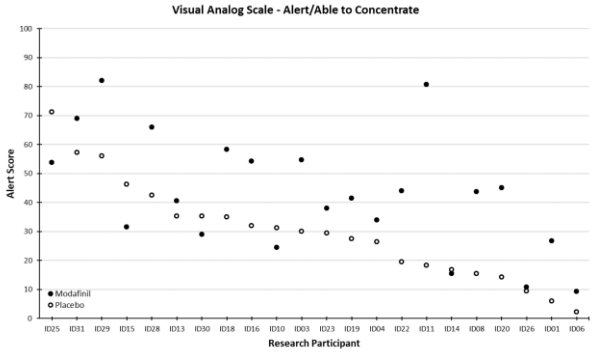

Wisconsin Card Sorting Task - Failure to Maintain Set
Modafinil
Placebo
Number Failures
Research Participant

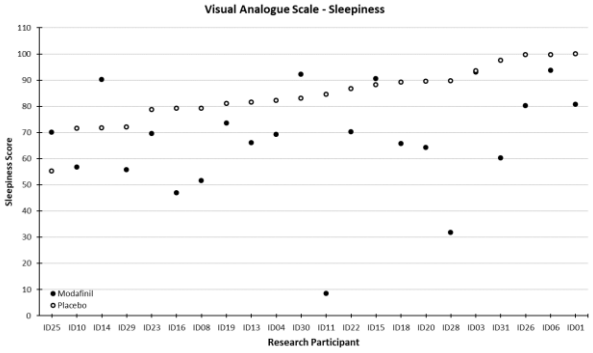

Oculaar PMI - Saccadic Velocity
Modafinil
Placebo
Saccadic Velocity (mm/s)
Research Participant

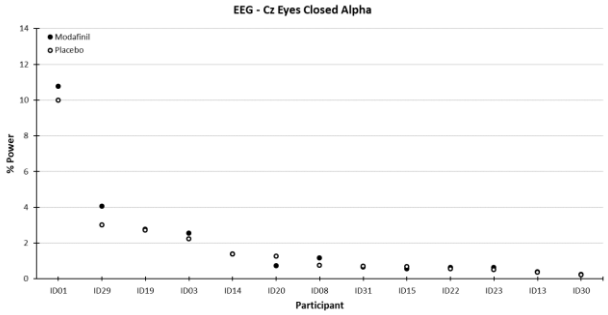

Ocular PMI - Constriction Latency
Modafinil
Placebo
Constriction Latency (ms)
Research Participant

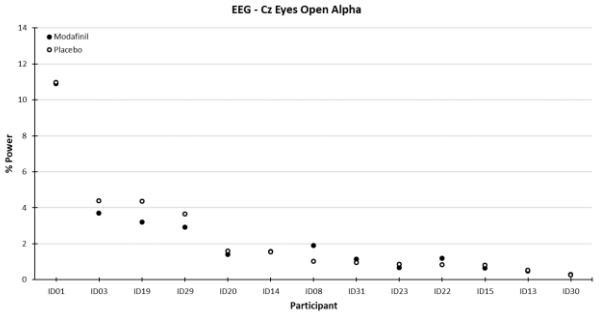

Profile of Mood States - Fatigue
Modafinil
Placebo
Fatigue Score
Research Participant

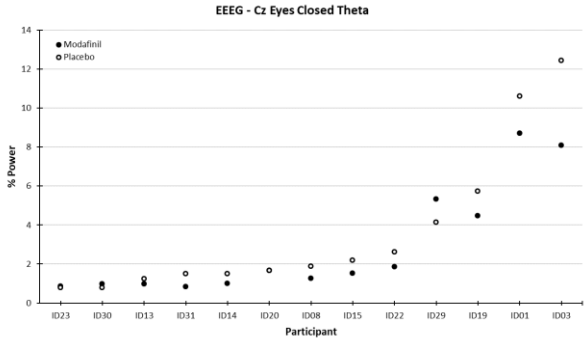

Profile of Mood States - Vigor
Modafinil
Placebo
Vigor Score
Research Participant

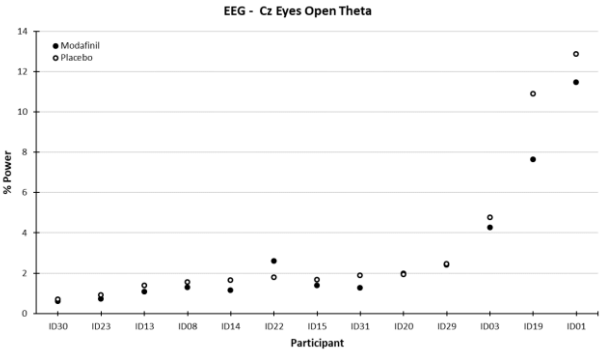

Visual Analog Scale - Alert/Able to Concentrate
Modafinil
Placebo
Alert Score
Research Participant

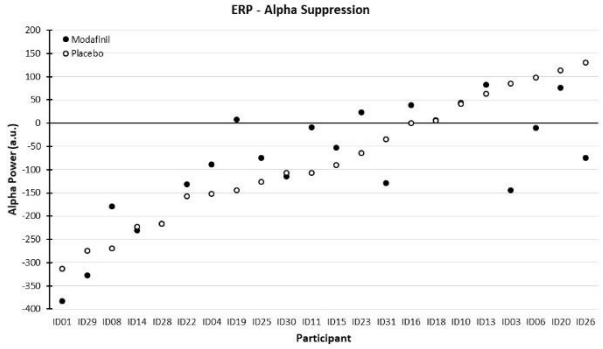

Visual Analogue Scale - Sleepiness
Modafinil
Placebo
Sleepiness Score
Research Participant


EEG - Cz Eyes Closed Alpha
Modafinil
Placebo
% Power
0
2
4
6
8
10
12
14
ID01 ID29 ID19 ID03 ID14 ID20 ID08 ID31 ID15 ID22 ID23 ID13 ID30
Participant


EEG - Cz Eyes Open Alpha
Modafinil
Placebo
% Power
0
2
4
6
8
10
12
14
ID01 ID03 ID19 ID29 ID20 ID14 ID08 ID31 ID23 ID22 ID15 ID13 ID30
Participant


EEEG - Cz Eyes Closed Theta
Modafinil
Placebo
% Power
0
2
4
6
8
10
12
14
ID23 ID30 ID13 ID31 ID14 ID20 ID08 ID15 ID22 ID29 ID19 ID01 ID03
Participant


EEG - Cz Eyes Open Theta
Modafinil
Placebo
% Power
0
2
4
6
8
10
12
14
ID30 ID23 ID13 ID08 ID14 ID22 ID15 ID31 ID20 ID29 ID03 ID19 ID01
Participant


ERP - Alpha Suppression
Modafinil
Placebo
Alpha Power (a.u.)
-400
-350
-300
-250
-200
-150
-100
-50
0
50
100
150
200
ID01 ID29 ID08 ID14 ID28 ID22 ID04 ID19 ID25 ID30 ID11 ID15 ID23 ID31 ID16 ID18 ID10 ID13 ID03 ID06 ID20 ID26
Participant