AFRL-HE-BR-TR-2004-0021

# United States Air Force Research Laboratory

## THE EFFICACY OF MODAFINIL AS AN OPERATIONAL FATIGUE COUNTERMEASURE OVER SEVERAL DAYS OF REDUCED SLEEP DURING A SIMULATED ESCAPE AND EVASION SCENARIO


Jeffery Whitmore
Brandon Doan
Tara Heintz
William Hurtle
James Kisner
Jennifer Smith

HUMAN EFFECTIVENESS DIRECTORATE
BIOSCIENCES AND PROTECTION DIVISION
FATIGUE COUNTERMEASURES BRANCH
2504 GILLINGHAM DRIVE
BROOKS CITY-BASE TX 78235

Joseph Fischer
Jonathan French
Patrick Hickey

NTI, Inc.
2504 GILLINGHAM DRIVE, STE 25
BROOKS CITY-BASE, TX 78235


April 2004


Approved for public release, distribution unlimited.



20040518 014

## NOTICES

This report is published in the interest of scientific and technical information exchange and does not constitute approval or disapproval of its ideas or findings.

This report is published as received and has not been edited by the publication staff of the Air Force Research Laboratory.

Using Government drawings, specifications, or other data included in this document for any purpose other than Government-related procurement does not in any way obligate the US Government. The fact that the Government formulated or supplied the drawings, specifications, or other data, does not license the holder or any other person or corporation, or convey any rights or permission to manufacture, use, or sell any patented invention that may relate to them.

The Office of Public Affairs has reviewed this paper, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This report has been reviewed and is approved for publication.

//SIGNED//

JEFFERY N. WHITMORE
Project Scientist

//SIGNED//

F. WESLEY BAUMGARDNER, Ph.D.
Deputy, Biosciences and Protection Division

# REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.

**1. REPORT DATE** *(DD-MM-YYYY)*
April 2004

**2. REPORT TYPE**
Interim

**3. DATES COVERED** *(From - To)*
Jun 2003 – Jan 2004

**4. TITLE AND SUBTITLE**
The Efficacy of Modafinil as an Operational Fatigue Countermeasure Over Several Days of Reduced Sleep During a Simulated Escape and Evasion Scenario

**5a. CONTRACT NUMBER**
F41624-97-D-6004

**5b. GRANT NUMBER**

**5c. PROGRAM ELEMENT NUMBER**
62202F

**5d. PROJECT NUMBER**
7757

**5e. TASK NUMBER**
P9

**5f. WORK UNIT NUMBER**
07

**6. AUTHOR(S)**
Whitmore, Jeffery (DR-III), Doan, Brandon (Maj), Fischer, Joseph (contr),
French, Jonathan (contr), Heintz, Tara (2Lt), Hickey, Patrick (contr),
Hurtle, William (Maj), Kisner, James (Capt), Smith, Jennifer (2Lt)

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**

Air Force Research Laboratory
Human Effectiveness Directorate
Biosciences & Protection Division
2504 Gillingham Dr. Ste 25
Brooks City-Base, TX 78235

NTI, Inc.
2504 Gillingham Dr. Ste 25
Brooks City-Base, TX 78235

**8. PERFORMING ORGANIZATION REPORT NUMBER**

**9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)**
Air Force Research Laboratory
Human Effectiveness Directorate
Biosciences & Protection Division
2504 Gillingham Dr. Ste 25
Brooks City-Base, TX 78235

**10. SPONSOR/MONITOR'S ACRONYM(S)**
AFRL/HE

**11. SPONSOR/MONITOR'S REPORT NUMBER(S)**
AFRL-HE-BR-TR-2004-0021

**12. DISTRIBUTION / AVAILABILITY STATEMENT**
Approved for public release; distribution is unlimited

**13. SUPPLEMENTARY NOTES**

**14. ABSTRACT**
The study presented was an assessment of the operational efficacy of modafinil for field environments, particularly focused on a type of environment which downed aircrew may encounter. This study was designed to examine the ability of modafinil to maintain alertness and performance over several days of reduced sleep in a field environment. The type of activity used in this study may be similar to some escape and evasion scenarios in which downed aircrew might find themselves. In addition, this type of environment and workload was similar to what some special forces personnel might experience. Results from this study will help in developing the operational guidelines for the special forces community and possibly provide support for the inclusion of modafinil in aircrew survival kits.
In general, the cognitive and sleepiness data support the hypothesis that modafinil would partially attenuate the performance decrements associated with fatigue (both sleep loss and circadian variation) in this study. The trends are fairly consistent across tests even though statistically significant differences between the conditions are intermittent. One of the most significant findings was the acceptance of modafinil amongst E & E experts was overwhelmingly high, with few side effects reported, and their unanimous agreement that modafinil was useful for field operations.

**15. SUBJECT TERMS**
Fatigue, Sustained Operations, Modafinil, Sleep Deprivation, Performance Enhancement

| 16. SECURITY CLASSIFICATION OF: UNCLASSIFIED | | | 17. LIMITATION OF ABSTRACT | 18. NUMBER OF PAGES | 19a. NAME OF RESPONSIBLE PERSON |
|---|---|---|---|---|---|
| a. REPORT | b. ABSTRACT | c. THIS PAGE | Unlimited | 29 | Maj Brandon Doan |
| Unclass | Unclass | Unclass | | | 19b. TELEPHONE NUMBER *(include area code)* (210) 536-8129 DSN 240-8129 |

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

## Table of Contents

**Background** ..... 1

**Methods** ..... 3

Participants ..... 3

Duration & Description of Study ..... 3

Instruments & Data ..... 4

Data Analysis ..... 5

**Results** ..... 6

**Discussion** ..... 19

**Conclusions** ..... 21

**Reference** ..... 21

**Attachment A** ..... 23

**Attachment B** ..... 24

## Figures

Figure 1. Four choice-Throughput Changes from Baseline ..... 7

Figure 2. Four Choice-Mean Reaction Time for Correct Responses Change from Baseline ..... 7

Figure 3. Logical Reasoning-Mean Reaction Time for Correct Responses Changes from Baseline ..... 8

Figure 4. Logical Reasoning-Standard Deviation for Correct Responses Changes from Baseline ..... 9

Figure 5. Logical Reasoning-Throughput Changes from Baseline ..... 9

Figure 6. Math-Mean Reaction Time for Correct Responses Change from Baseline ..... 10

Figure 7. Math- Standard Deviation for Correct Responses Changes from Baseline ..... 11

Figure 8. Math- Throughput Changes from Baseline ..... 11

Figure 9. Continuous Processing Task-Accuracy Changes from Baseline ..... 12

Figure 10.Continuous Processing Task-MRTC Changes from Baseline ..... 13

Figure 11.Continuous Processing Task- Throughput Changes from Baseline ..... 13

Figure 12. Sleep Scale-Changes from Baseline ..... 14

Figure 13. Diastolic Blood Pressure-Changes from Baseline ..... 15

Figure 14. Systolic Blood Pressure- Changes from Baseline ..... 15

Figure 15. Heart Rate- Changes from Baseline ..... 16

Figure 16. Oral Temperature- Changes from Baseline ..... 16

Figure 17. Jump Task-Jump Height Changes from Baseline ..... 17

Figure 18. Jump Task-Explosive Leg Factor Changes from Baseline ..... 18

Figure 19. Jump Task-Ground Time Changes from Baseline ..... 18

**Background**

Fatigue is well established in causing significant decrements in performance. In the aviation environment, performance decrements on long duration missions may lead to outcomes ranging from severe crew discomfort, to mission degradation, to loss of an aircraft. Conservative fatigue countermeasures may prove insufficient to counter the effects of extremely long-duration missions required in current Air Force air and ground operations. Dextroamphetamine has a good track record in countering fatigue, but has some undesirable side effects (e.g., agitation, inability to nap, addictive attributes). Modafinil has received considerable study in the aviation environment and appears to be effective at significantly extending performance during conditions of sleep-loss, with a relatively low incidence of side effects and its overall reduced risk (modafinil is a schedule IV controlled substance versus dextroamphetamine which is a schedule II). The study presented here was an assessment of the operational efficacy of modafinil for field environments, particularly focused on a type of environment which downed aircrew may encounter.

This study was designed to examine the ability of modafinil to maintain alertness and performance over several days of reduced sleep in a field environment. This setting was chosen to simulate several operational environments. First, the type of activity used in this study may be similar to some escape and evasion scenarios in which downed aircrew might find themselves. In addition, this type of environment and workload was similar to what some special forces personnel might experience. Thus, information gained from this study will be used for multiple purposes. Results from this study will help in developing the operational guidelines for the special forces community and possibly provide support for the inclusion of modafinil in aircrew survival kits.

In December 1998, the pharmaceutical company Cephalon received FDA approval to market a new vigilance-enhancing drug, modafinil (Provigil®), for the management of narcolepsy. This drug belongs to a new group of drugs called "eugregorics" that have been under development for over ten years and marketed in France since 1993 and the United States since 1998. Modafinil mimics the effects of amphetamines by producing a high quality of wakefulness, but lacks the typical negative side effects associated with amphetamines (Lagarde, Batéjat, Van Beers Sarafian and Pradella, (1995). The neuro-chemical mechanism of modafinil is not yet fully understood, but modafinil is known to affect the alpha-1 adrenergic receptors, akin to the neurotransmitter norepinephrine. Modafinil does not work by inhibiting reuptake; instead it directly stimulates the norepinephrine receptors (Cephalon, 1998). Lin, Hou, Rambert, and Jouvet (1997) found modafinil both chemically and pharmacologically different from amphetamines in that modafinil produces long lasting waking effects without behavioral modification, addictive attributes, or sleep rebound. In addition to its lack of adverse effects, modafinil exhibits a terminal half-life of 9-14 hrs with peak blood concentrations 2-4 hrs after absorption with an oral clearance of 50-60 mL/min (Wong, Gorman, McCormick, & Grebow, 1997). This profile makes modafinil a prime candidate for operational use in situations requiring sustained wakefulness. This application is now being recognized in the commercial sector as an FDA advisory panel has recently (Sep 2003) recommended modafinil to be approved for the treatment of excessive sleepiness associated with obstructive sleep apnea and shift-work sleep disorder.

Several studies ( Bensimon, Benoit, Lacomblez, Weiller, Warot, Weial and Puech, 1991; Lagarde and Batejat, 1995; Batéjat and Lagarde, 1999) clearly demonstrated that 200 mg of modafinil administered either in a single dose or repeated every 8-hrs for longer periods of arousal significantly enhanced performance during periods of sleep deprivation. More recent investigations have focused on the effectiveness of 100 mg doses. In a study by Baranski, Cian, Esquivie, Pigeau,

& Raphel (1998), subjects given a dosage of 100 mg every eight hours, over a 24-hour period, maintained cognitive performance levels throughout 64 hours of sleep deprivation. Subjects given 50 mg every eight hours, over a 24-hour period, maintained non-significant performance improvement when compared to placebo. Stivalet, Esquivie, and Barraud (1998) studied the effects of modafinil on attentional processing during 60 hours of sleep deprivation. Subjects were given a total of 300 mg/day in 100 mg doses every 8 hours. Results indicated that modafinil prevented both slowing of serial processing and the normal increases in the rate of error during the period of sleep deprivation. A recent study performed at Brooks City-Base by Whitmore (2002) kept participants awake for 88-hrs while they received either 100 mg or 200 mg every 8 hours (nine total doses). Few side effects were observed in the study and performance was relatively well maintained through 3 days and 2 nights of sleep deprivation (approximately the first 60-hrs). Performance for both drug conditions was better than that under an historical no-drug condition; however, both drug conditions suffered significant performance degradation on the third night of sleep-loss.

Research into possible unfavorable side effects of modafinil (Morehouse, Broughton, Fleming, George, and Hill, 1997) found subjects reported 52 adverse effects, yet none were statistically different from the placebo group. More subjects complained of nervousness and nausea in the 400 mg/day group, although this was not statistically different from the 200 mg/day group. Phase 3 clinical trials have confirmed that the only adverse effect more frequent in the 400 mg/day group was headache. Doses of 800 mg/day produced elevations in blood pressure and pulse rate. Pigeau, Naitoh, Buguet, McCann, Baranski, Taylor, Thompson, & Mack (1995) reported an increased frequency of urination when compared to dextroamphetamine or placebo. Caldwell and Caldwell (2000) reported anecdotal evidence of increased vestibular complaints (i.e. dizziness) in a study involving three 200 mg doses given at 4-hr intervals. An evaluation of this phenomenon conducted by Eddy (2001) and performed at Brooks AFB, TX showed no negative vestibular effects associated with a single 400 mg dose of modafinil.

Modafinil studies have also examined sleep rebound effects. Batéjat (1999) examined napping and modafinil as two countermeasures for fatigue. Results indicate both were beneficial, and demonstrated modafinil did not prevent sleep as has been found with the use of amphetamines. Two studies utilized modafinil during prolonged sleep deprivation, then measured sleep rebound parameters via EEG for two nights afterward. Lagarde et al. (1995) found modafinil in 600 mg/day doses produced a sleep rebound effect on the second post-treatment night. Buguet, Montemayeur, Pigeau, and Naitoh, (1995), showed modafinil in 300 mg/day levels did not produce any sleep rebound effect. In summary, the efficacy of modafinil to reduce or prevent sleep-loss induced performance decrements has been proven. The clinical safety of modafinil has also been proven. This effort was an assessment of the operational utility of modafinil.

In 1997, Baranski and Pigeau found that modafinil produced "a disruptive effect on self-monitoring, inducing a reliable 'overconfidence' effect which was particularly marked 2-4 hours post-dose (100mg dose)." Batejat et al. (1999) also reported modafinil related changes in self-confidence. Eddy's Brooks AFB study has shown no post-drug effects on confidence for up to 6-hrs post dose when asking subjects to estimate performance on various performance tasks.

The recent modafinil study completed by Whitmore evaluated the alerting efficacy of modafinil (100 mg and 200 mg every 8-hr / 300 mg or 600 mg per day) in an 88-hr sleep deprivation laboratory study. All participants, save one (who experienced elevated blood pressure), well tolerated the repeated modafinil dosing. The subjective symptom data revealed no case where a severe symptom was attributable to modafinil. Most adverse reactions, such as 'difficulty

focusing,' were attributable to staying awake for 88-hrs (i.e., these types of symptoms were typically reported on the 2nd and 3rd night of the study). Overall performance on several tasks was maintained better by the 200 mg condition than by the 100 mg condition. In general however, neither dose of modafinil was adequate to maintain performance during the 3rd night of testing.

This study was designed by survival instructor personnel to include key elements of several operational environments. Outside of data collection and modafinil dosing, nothing occurs in this study that does not or cannot otherwise occur in the operational training environment. This study was funded by the United States Special Operations Command , Biomedical Initiatives Steering Committee.

The objective of this effort was to evaluate the efficacy of modafinil for sustaining alertness in personnel involved in sustained field operations (3 days of reduced sleep). Information from this study may be used to modify existing operational guidelines regarding Escape and Evasion (E & E) and Special Operations Forces (SOF) operations to include modafinil use, with the purpose of providing a performance advantage to our troops who must perform critical operations involving little or no sleep for several days.

It was expected that modafinil would enhance objective performance and reduce negative affect when compared to the placebo condition throughout the course of the study. The differences in performance between conditions should be most apparent on nights two and three of the study. Few to no side effects were anticipated in the modafinil group beyond the normal side effects seen with sleep loss.

**Methods**

*Participants*

Twenty USAF Survival Training Specialists volunteered as the participants for this study by signing an informed consent form. All participants were from the 336th Training Group at Fairchild AFB. Participation was voluntary and no financial compensation was offered. Participants were male, between the ages of 18 and 34. All participants underwent a medical examination to ensure they were fit to participate in the study. The medical examination included: a review of the potential participants medical history, and blood and urine tests to allow assessment that liver and kidney function were within normal parameters. Participants also underwent a similar medical examination post-data collection. This research was approved by the Air Force Surgeon General #F-BR-2003-0044-H

*Duration & Description of Study*

The primary data collection period occurred over a 65-hr field event established for this study. Additionally, sleep and subjective fatigue data collection, and a single daily cognitive test administration (requiring approximately 10-min of time per day to complete) were performed three days prior to and post termination of the field event. A 2-hr training/orientation session was conducted the week prior to the field event. See Attachment A for an experimental schedule.

During the field event, participants were formed into teams of two. One person on each team received modafinil, the other placebo. Drug administration was double-blind and assignment of condition to participant was done randomly. Those in the modafinil condition received 100 mg of modafinil at those times indicated in Attachment A, with a maximum daily dosage of 300 mg. Those in the placebo condition received an identically appearing inert capsule at the same times. Due to testing logistics, five teams performed the field event one week and the other five teams the

next week. Since counterbalancing was done per team there should not be a week effect for the drug conditions.

Participants performed simple navigation as they followed a route in the general shape of a star with a base camp at the top. Teams were launched between 15- and 30-min intervals and maintained this separation throughout the route. Participants hiked approximately 22 miles over the first two days of the field event and then bivouacked for the remaining 24 hrs of the study. While traveling the route, participants performed 10-min of tests every 3-hrs. This test block consisted of several simple cognitive tests performed on a personal digital assistant palmtop computer (PDA), a subjective sleepiness check, a fatigue questionnaire, a mood questionnaire, and a verbal memory task accomplished over the radio. Every 6-hrs along the route there was a checkpoint. At each checkpoint the normal 10-min 3-hr test block was performed alongside some additional testing. This additional testing included a symptom survey/health check, saliva sampling, a jump test, a decision-making test, and a blood pressure/heart rate check. Given the number of tests and the staggered launch of teams, a checkpoint block that began at 1200hrs for the first team would not be completed until 1500hrs for the fifth team. Participants were not allowed to sleep during the first night on the route and were only allowed a 2-hr sleep period during their second and third night on the route. Each participant carried a light backpack consisting of rations, water, and sundry provisions. As mentioned previously, prior to the start of data collection a 2-hr training session was conducted. During the training session participants were trained to asymptotic performance on the cognitive tests.

*Instruments and Data*

The following data collection instruments were applied at the times indicated in Attachment A:

- *Actigraph:* An actigraph was issued to each participant. The actigraph resembles a wristwatch and is worn in a similar manner. A small accelerometer systematically records the individual's movement over time, both while awake and asleep, allowing for the objective identification of sleep/wake patterns. The data are also sensitive to the quality of sleep, showing less activity during more restful sleep. Each participant wore an actigraph for three days prior to, during, and three days following the field event.
- *Questionnaires*: A demographic intake questionnaire was given to each participant at the orientation meeting.
- *Activity Log*: Each participant was provided with a log on which to record his wake rest times. Sleep intervals were self-recorded as they occurred throughout the data collection period. Subjective rating scales were also provided to periodically register self-estimates of sleepiness and fatigue.
- *Cognitive Performance Battery (ARES)*: Math Processing (simple serial mathematical problems), Logical Reasoning (respond true/false to a single statement describing the relation of a pair of symbols), Four Choice Reaction Time (tap the illuminated quadrant), and a Continuous Processing task (determine whether current number is the same as the previous value and memorize current number for comparison to next value) were administered on a PDA. The ARES battery required about 7-min to complete and was administered every 3-hrs during the field event. We used response accuracy, mean reaction time for correct responses (MRTC), standard deviation for correct response time (SDRTC), and throughput (correct responses per minute) as the outcome measures from each ARES task.

- *Radio Memory Task*: A simple verbal memory task was performed every three hours during the field event. This test was insensitive to the effects of fatigue and will not be discussed in this paper.
- *Jump Test:* A standing vertical jump test comprised of 16 jumps was given at every checkpoint. Jump height, explosive leg factor (ELF - a combination of jump height and ground dwell time), and ground dwell time were used as the outcomes for this test.
- *Subjective Assessment*: Sleepiness was recorded every 3-hrs using a computerized version of the Stanford Sleepiness Scale. An additional fatigue questionnaire (The Sustained Operations Assessment Profile, SOAP) was given every 3-hrs on the PDA. The results from the SOAP are not complete and will not be reported in this paper. Approximately 2-min were required to complete each questionnaire.
- *Salivary measures:* A small amount of saliva (2-3cc) was collected at each checkpoint to assess melatonin and protein amylase levels. These results are also not complete at this time and will not be reported in this paper.
- *Vitals:* Diastolic blood pressure (DBP), systolic blood pressure (SBP), heart rate, and oral temperature were collected at each checkpoint.

During the field data collection portion of the study, several measures were taken to ensure the safety of the participants. Each team of participants was issued a hand-held radio. The radio was used between checkpoints for a safety check-in and brief memory task. Participants were formed into teams of two to allow a buddy-system type of approach. Participants were also individually issued a GPS tracking unit. This tracking unit allowed a participants location to be ascertained at any point on the route but did not provide navigational information. Checkpoints were laid out on the route at 6-hr intervals. As participants paused at these checkpoints to perform additional testing or to sleep, they were queried as to their overall subjective and health state. The route was checked by survival instructor personnel for dangerous/difficult obstacles. A physician or physician's assistant was located at the base camp for the duration of the field event.

*Data Analysis*

Before any statistical analyses were performed, the data was baseline-adjusted to counter any potential inherent differences between the drug groups. This was accomplished for each outcome measure by subtracting a participant's baseline trial (Day 1 1800 hrs) from each of the subsequent trials. All statistical testing was based upon these "deltas". To ensure data quality, only data collected at the 12 checkpoints along the route (where testing conditions could be monitored and closely controlled) were used in the analyses.

For each continuous, normally distributed measure, a repeated measures analysis of variance (ANOVA) was performed to test for significant drug main effects and/or drug by time interaction. A Huyhn-Feldt adjustment was made for variables that failed Mauchly's Test of Sphericity. When significant effects were detected in the ANOVAs, post-hoc simple effects tests (Winer, pg. 174) were used to compare the modafinil change from baseline with the placebo change from baseline at each time point, separately. In addition, the mean at each time point was compared back to the mean at baseline for the placebo and modafinil groups, separately. For ordinal outcome measures, Mann-Whitney U-tests were used to compare the drug and placebo conditions for differences in the change from baseline at each of the checkpoints, separately.

Sample Size Determination: The primary tests of interest were the post-hoc comparisons of the two drug conditions at specific time points. Consequently our power analysis for determining

sample size was based on those tests. A sample of 10 participants per group would provide approximately a 57% chance (power) of detecting differences that are about 1 standard deviation in magnitude, when testing at the 0.05 two-tailed alpha level. While this is considered a relatively low power for most research studies, this study provided a unique opportunity to examine modafinil in the field. Thus while the chance of finding significant effects are low, those that are found are particularly meaningful and trends in the data would provide valuable direction for future studies.

**Results**

Due to difficulties with the PDA's there was insufficient data for two of the participants (both in the modafinil group), thus they were removed from the analysis of the computerized performance data. Additionally one participant (also in the modafinil group) forgot to take a single dose and was removed from all data analyses. For the remaining participants we lost about 3% of the performance data. This data was estimated (based upon the average percent change of the other data available at a particular time) to facilitate the statistical procedures.

Sleep – The average amount of sleep obtained for the three nights prior to the field event did not significantly differ between the placebo and modafinil groups (placebo = 7.3hrs, modafinil = 7.8hrs). Likewise, there was no difference in the total sleep obtained during the 65-hrs in the field (placebo = 6.35hrs, modafinil = 5.5hrs).

Attachment B contains the descriptive statistics and statistical test results for this study. For each outcome measure the baseline mean and standard deviation are shown followed by the mean change (and standard deviation) from baseline at each checkpoint. The ANOVA results are shown in the last three columns of the table. For those variables where an ANOVA indicated significance drug effects, superscripts (defined in the table legend) are used to identify significant post-hoc results. If only simple time effects were present for an outcome measure, no post-hoc testing was performed. Only variables for which significant effects were observed ($p \leq 0.05$) or which showed a strong trend and approached significance ($p \leq 0.10$) will be discussed and graphed in the text below.

Four Choice – For throughput the drug main effect approached significance ($p = 0.067$) and the main effect of time was significant ($p = 0.007$). Figure 1 shows the modafinil means tend to remain at about baseline level and are generally higher than placebo means with marginally significant differences ($p<0.10$) at two time points. When comparing each time point to baseline, the changes were marginally worse at only one time point for modafinil, and significantly or marginally worse at seven time points for placebo. Refer to Attachment B for specific post-hoc differences. MRTC showed only a main effect of time ($p = 0.001$). Inspection of Fig 2 gives no clear indication of a general fatigue pattern over the duration of the study (i.e., a linear trend resulting from sleep loss) but instead shows performance to be impacted generally by circadian variation and, by sleep inertia at one point (Day 4 0200). While the ANOVA did not detect significant drug effects, the relationship of the patterns seen for the two drug conditions is similar to those seen for throughput.

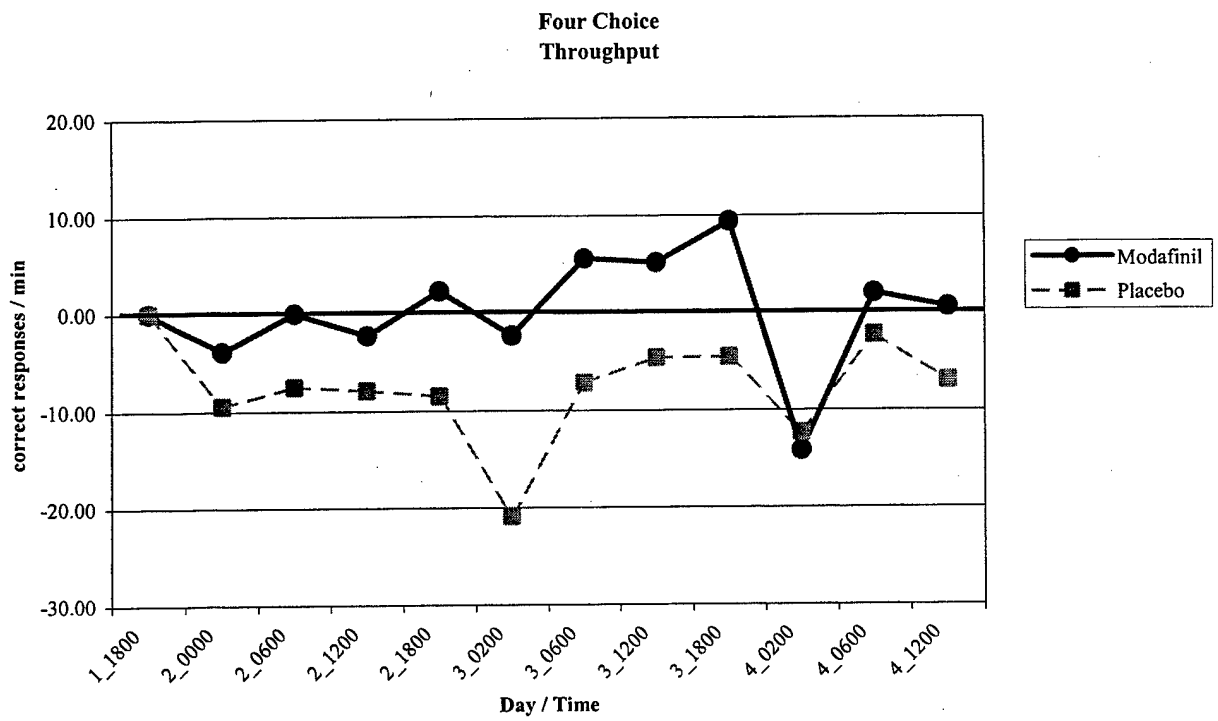


Figure 1 Four Choice - Throughput Changes from Baseline
Baseline values: Modafinil = 161, Placebo = 174

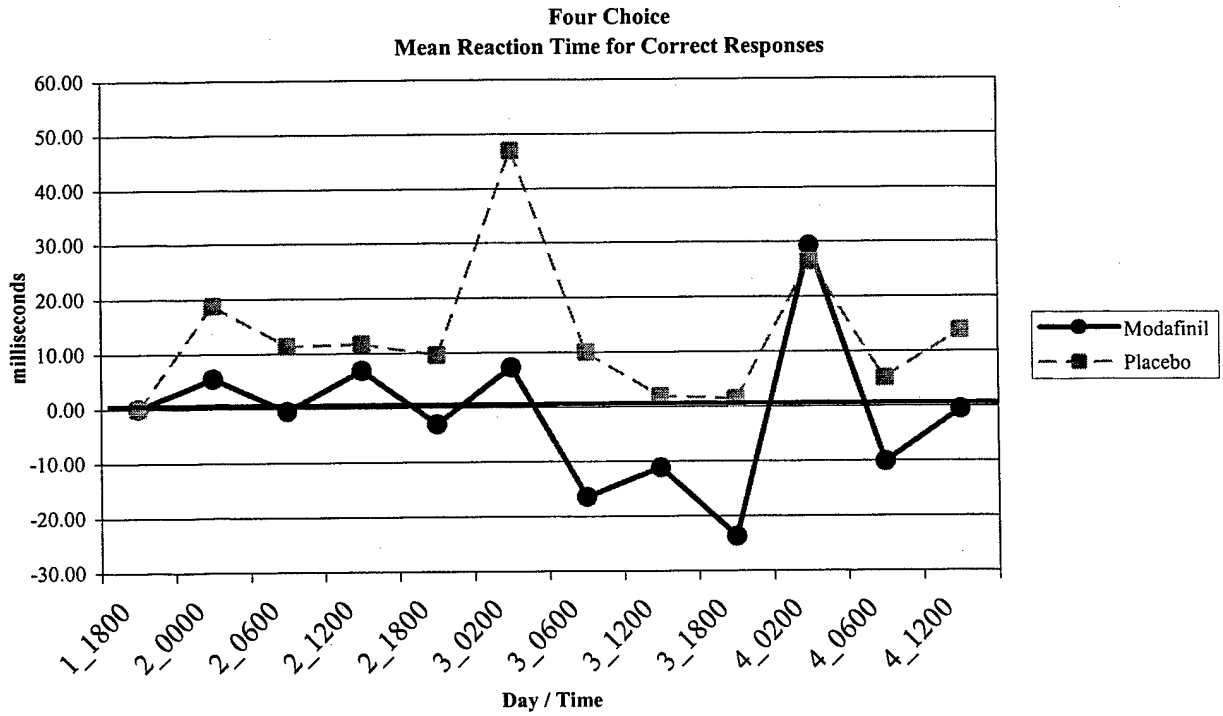


Figure 2 Four Choice - Mean Reaction Time for Correct Responses Changes from Baseline
Baseline values: Modafinil = 376, Placebo = 346

Logical Reasoning – For MRTC, SDRTC, and throughput, there were drug by time interactions ($p = 0.074$, $p = 0.098$, $p = 0.020$ respectively) and time main effects ($p = 0.005$, $p = 0.004$, and $p<0.001$, respectively). In Figure 3, MRTC performance under modafinil appears to be better than placebo from Day 2 1200 onwards, and was marginally, or significantly, better at two time points. Furthermore, modafinil was not found to change significantly from baseline at any time point, whereas placebo was marginally worse at three time points. Modafinil SDRTC performance in Fig 4 is shown to be equal to or better than placebo performance from Day 2 1200 onwards and was significantly better at one time point. Modafinil performance was not found to change significantly from baseline at any time point while placebo performance was marginally degraded at one time point. In Figure 5, throughput performance under modafinil appears to be better than placebo from Day 2 1200 onwards, and was significantly better at two time points. Placebo throughput was marginally lower than baseline at two time points whereas modafinil throughput generally remained near baseline or improved (one improvement was marginally significant).

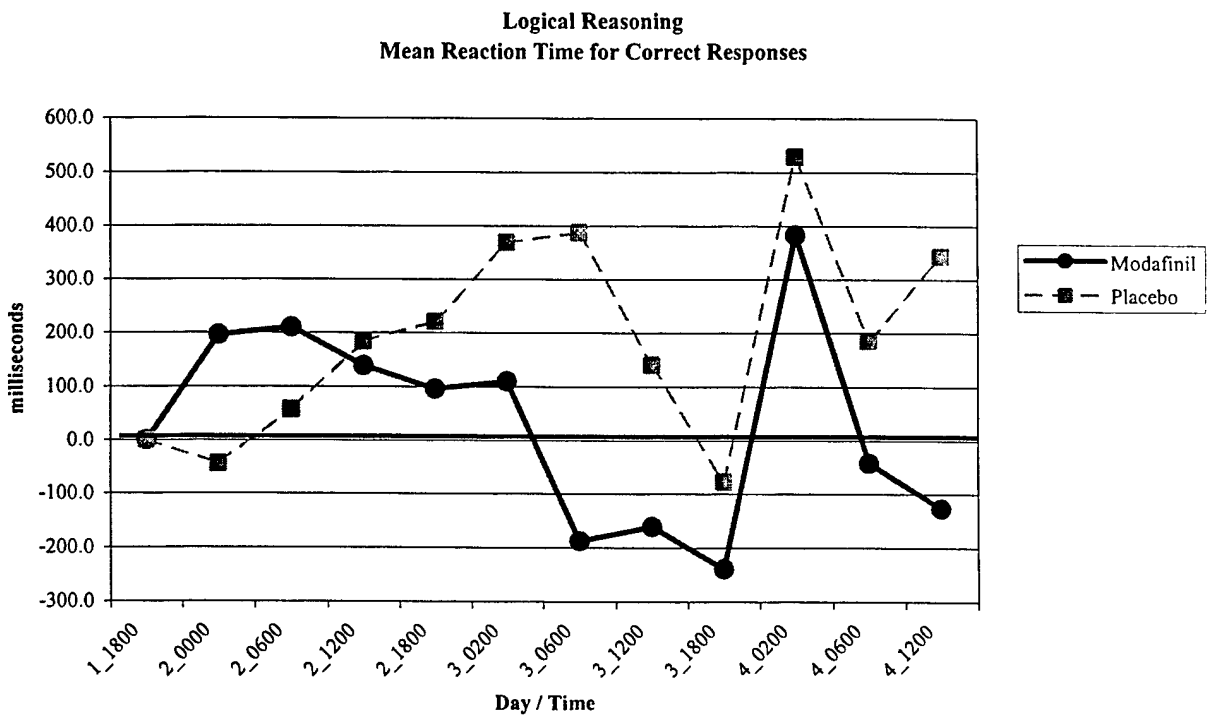


Figure 3 Logical Reasoning - Mean Reaction Time for Correct Responses Changes from Baseline
Baseline values: Modafinil = 2062, Placebo = 1925

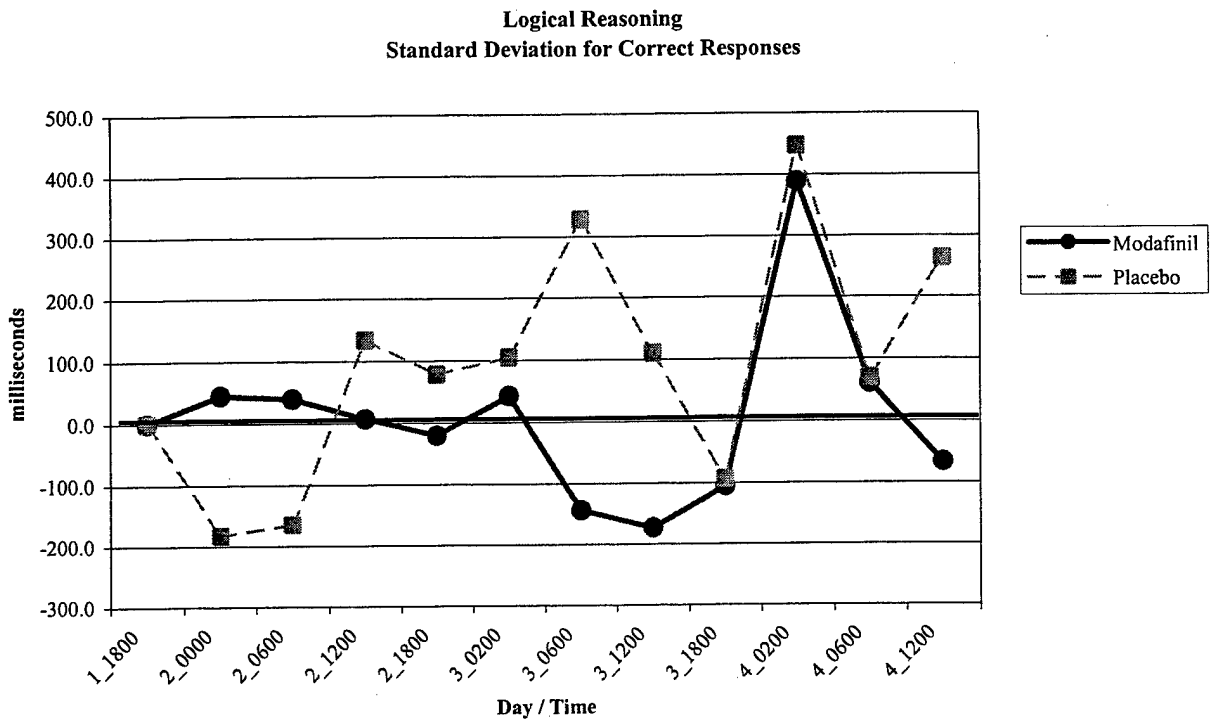


Figure 4 Logical Reasoning - Standard Deviation for Correct Responses Changes from Baseline
Baseline values: Modafinil = 894, Placebo = 853

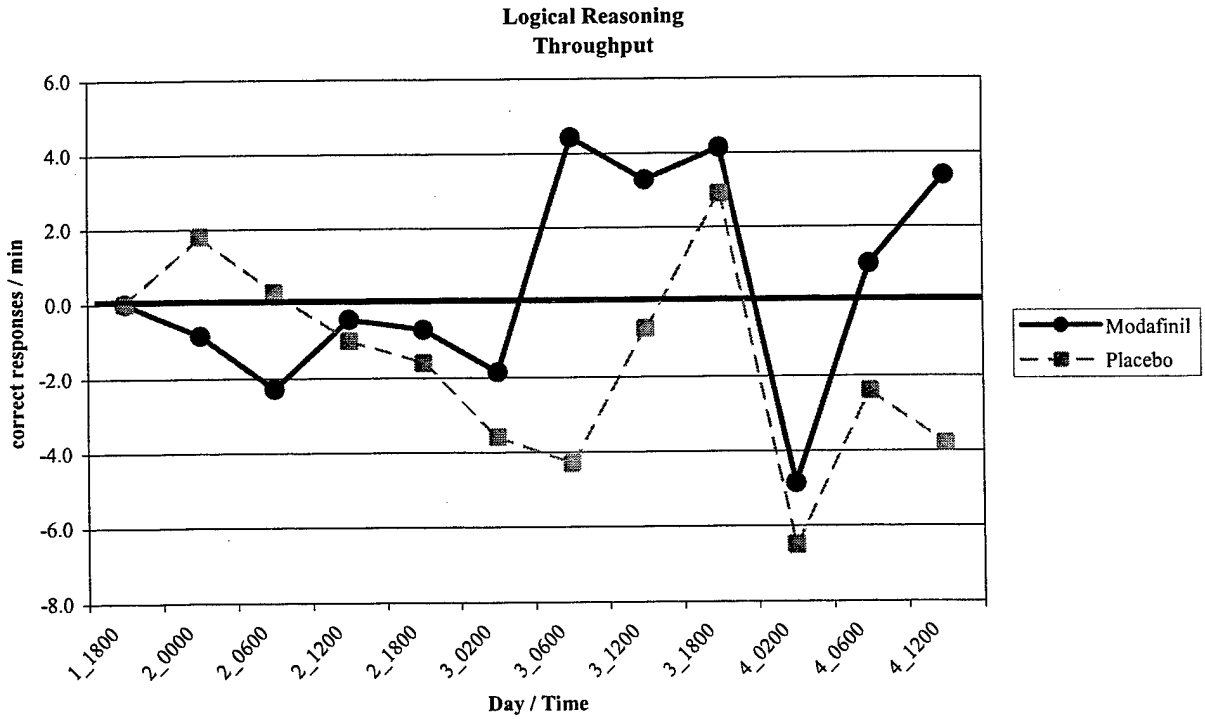


Figure 5 Logical Reasoning - Throughput Changes from Baseline
Baseline values: Modafinil =27.9, Placebo = 29.8

Mathematical Processing – For MRTC the drug main effect approached significance ($p = 0.073$) and the time main effect was significant ($p = 0.006$). Figure 6 shows the modafinil means tend to improve over time from baseline level and are lower than placebo means. Modafinil showed two marginal improvements and two significant improvements over placebo. Upon comparison to baseline modafinil was significantly faster at one time point and marginally faster at two others while placebo was significantly slower at three. SDRTC and throughput were shown to have significant time main effects ($p = 0.043$ and $p<0.001$, respectively). SDRTC (see Fig 7) shows the familiar circadian and sleep inertia effects. Throughput shows a slight learning trend over the course of the study (see Fig 8), primarily due to the modafinil means, and it also reflects the negative early morning/sleep inertia effect at Day 4 0200.

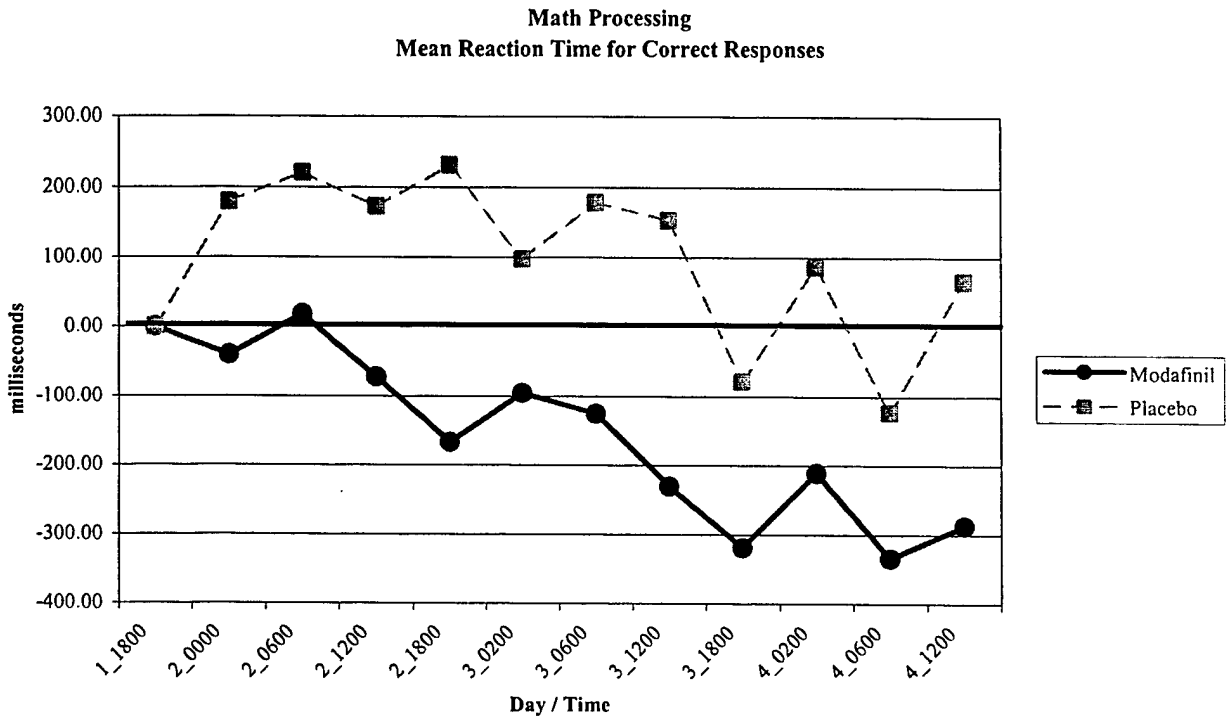


Figure 6 Math - Mean Reaction Time for Correct Responses Changes from Baseline
Baseline values: Modafinil = 2191, Placebo = 1881

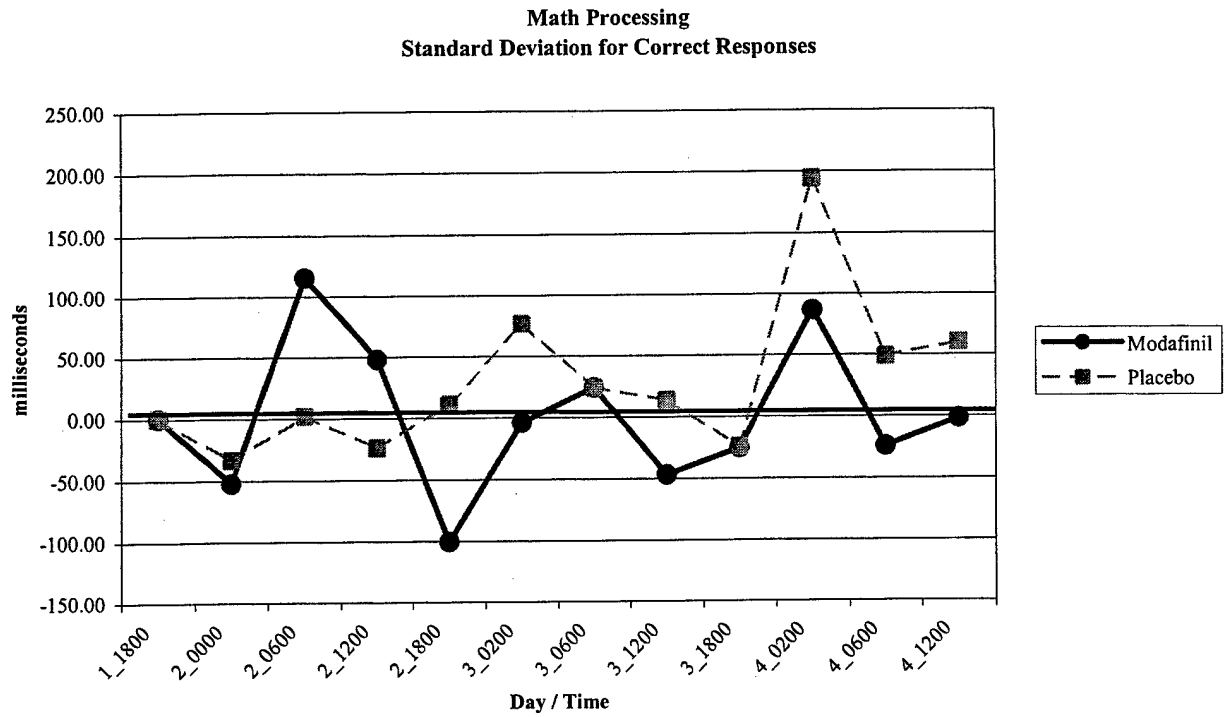


Figure 7 Math - Standard Deviations for Correct Responses Changes from Baseline
Baseline values: Modafinil = 676, Placebo = 670

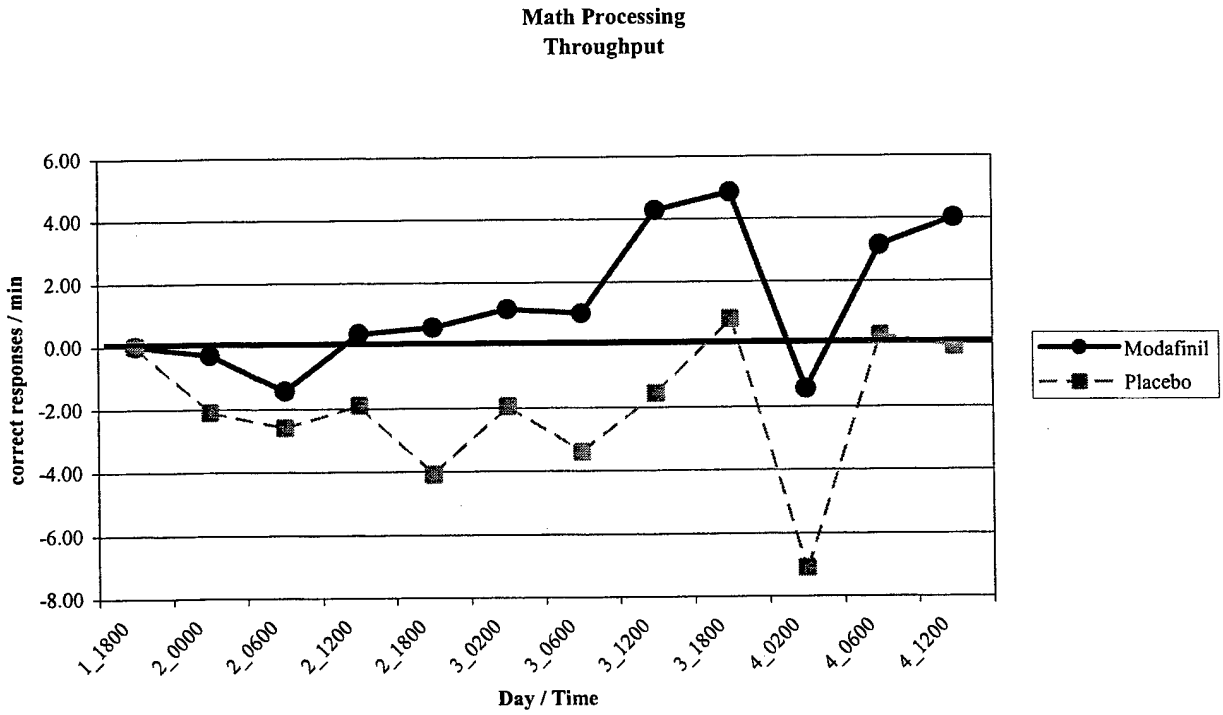


Figure 8 Math - Throughput Changes from Baseline
Baseline values: Modafinil = 26.6, Placebo = 30.0

Continuous Processing - No significant drug effects were found for any of the outcome measures of this test. A main effect of time was nearly significant for accuracy ($p = 0.054$), and was significant for MRTC ($p<0.001$), and throughput ($p = 0.007$). Fig 9 shows a slight downward trend for accuracy over the course of the study for both drug conditions. MRTC (see Fig 10) shows a very strong circadian variation for both groups; however, modafinil performance is never worse than baseline. Throughput also shows circadian variation (see Fig 11)and the infamous Day 4 0200 effect.

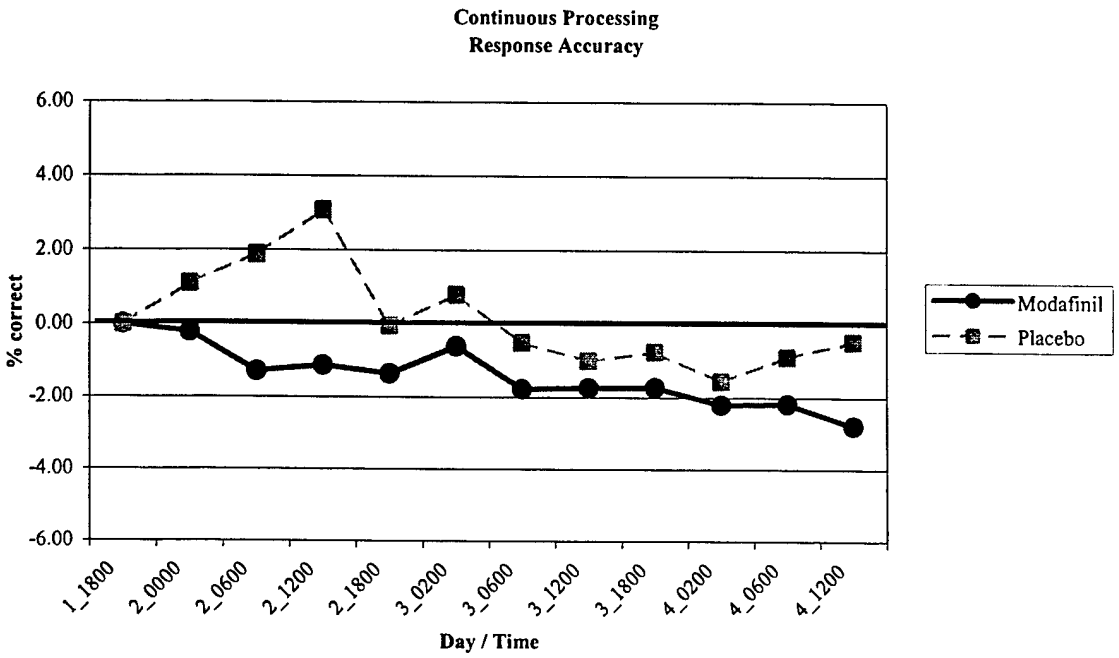


Figure 9 Continuous Processing Task - Accuracy Changes from Baseline
Baseline values: Modafinil = 98.7, Placebo = 94.4

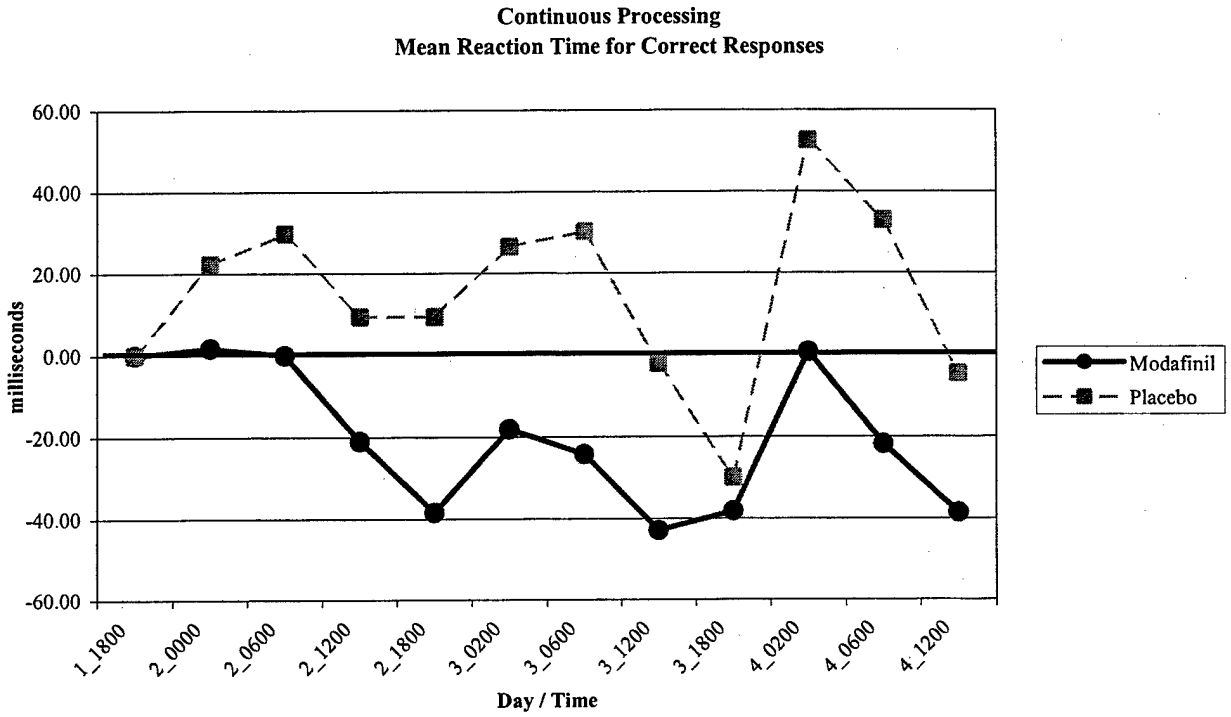


Figure 10 Continuous Processing Task - MRTC Changes from Baseline
Baseline values: Modafinil = 479, Placebo = 426

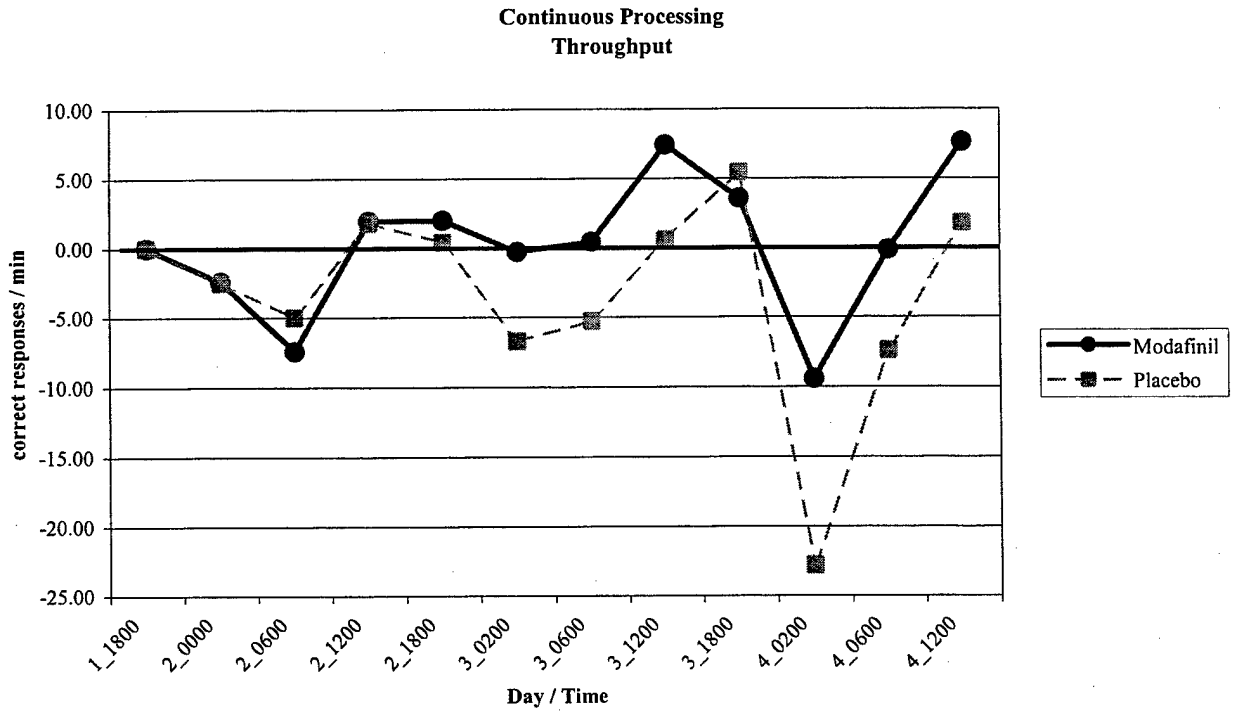


Figure 11 Continuous Processing Task - Throughput Changes from Baseline
Baseline values: Modafinil = 110, Placebo = 115

Sleep Scale - A significant drug by time interaction was detected for the sleep score (p=0.004). The sleep score also showed a main effect of time (p<0.001). Figure 12 shows a mixed trend with the modafinil group maintaining a lower sleepiness than placebo from Day 3 0600 onwards. There were only two time points at which the modafinil change was significantly lower than the placebo change. Interestingly, when comparing each time point to baseline, the changes were significantly worse at all but one point for placebo, and were significantly worse at only six of the times for modafinil.

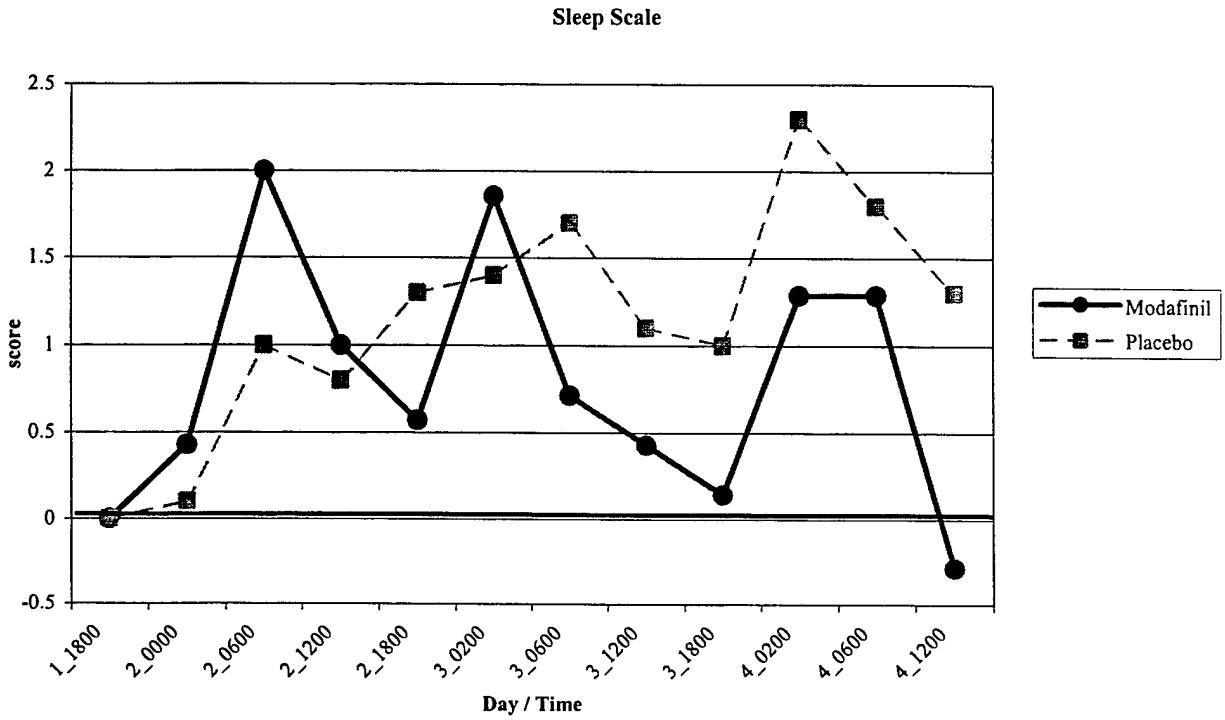


Figure 12 Sleep Scale - Changes from Baseline
Baseline values: Modafinil = 1.9, Placebo = 1.7

Vitals - For DBP, a significant drug main effect was detected (p=0.030) as well as a significant main effect of time (p=0.042). Under modafinil DBP was at or above baseline levels whereas placebo DBP was at or below baseline levels (see Fig 13). Two significant differences and two marginally significant differences between the conditions were observed. When compared to baseline modafinil was significantly higher at one time point and marginally higher at another. Placebo results indicated five time points where DBP was lower than baseline. There were significant time effects for SBP, heart rate, and temperature (p=0.01, p<0.001, and p<0.001, respectively). Generally there was a slight increase of SBP over the course of the study (Fig 14). Heart rate showed clear circadian effects with little difference between the groups (Fig 15). Oral temperature also showed clear circadian variation (Fig 16) with modafinil being consistently slightly higher; however, never higher than baseline.

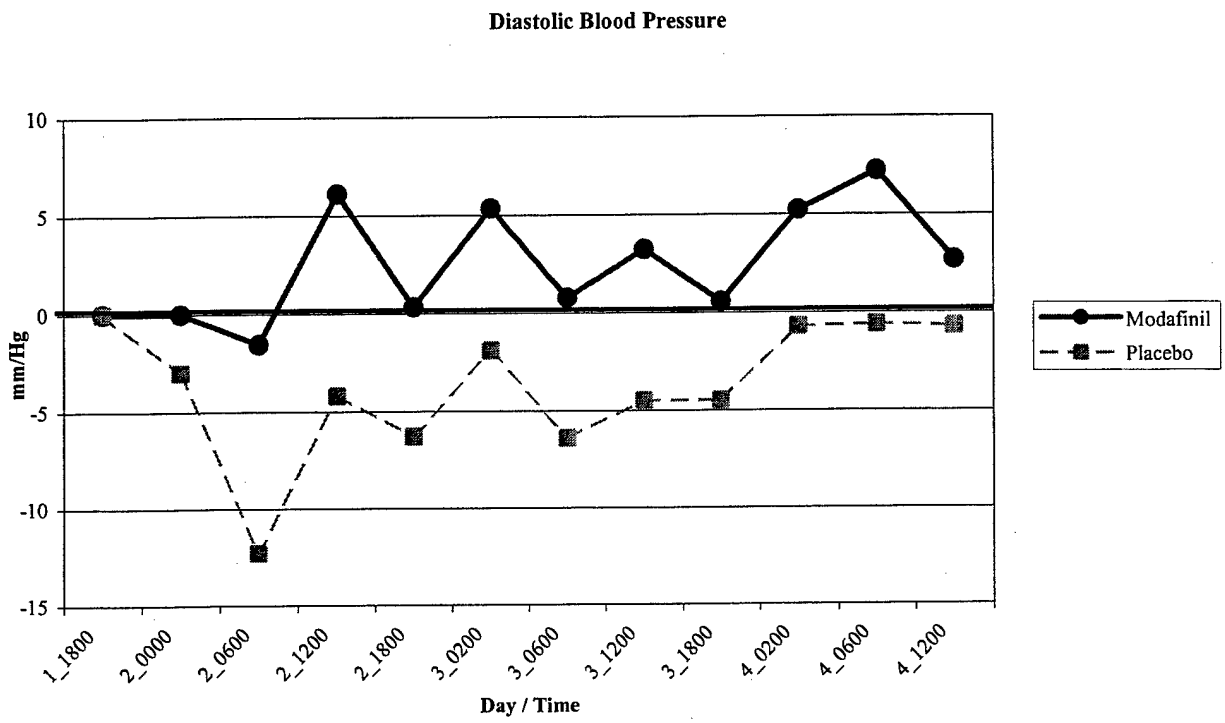


Figure 13 Diastolic Blood Pressure - Changes from Baseline
Baseline values: Modafinil = 75, Placebo = 83

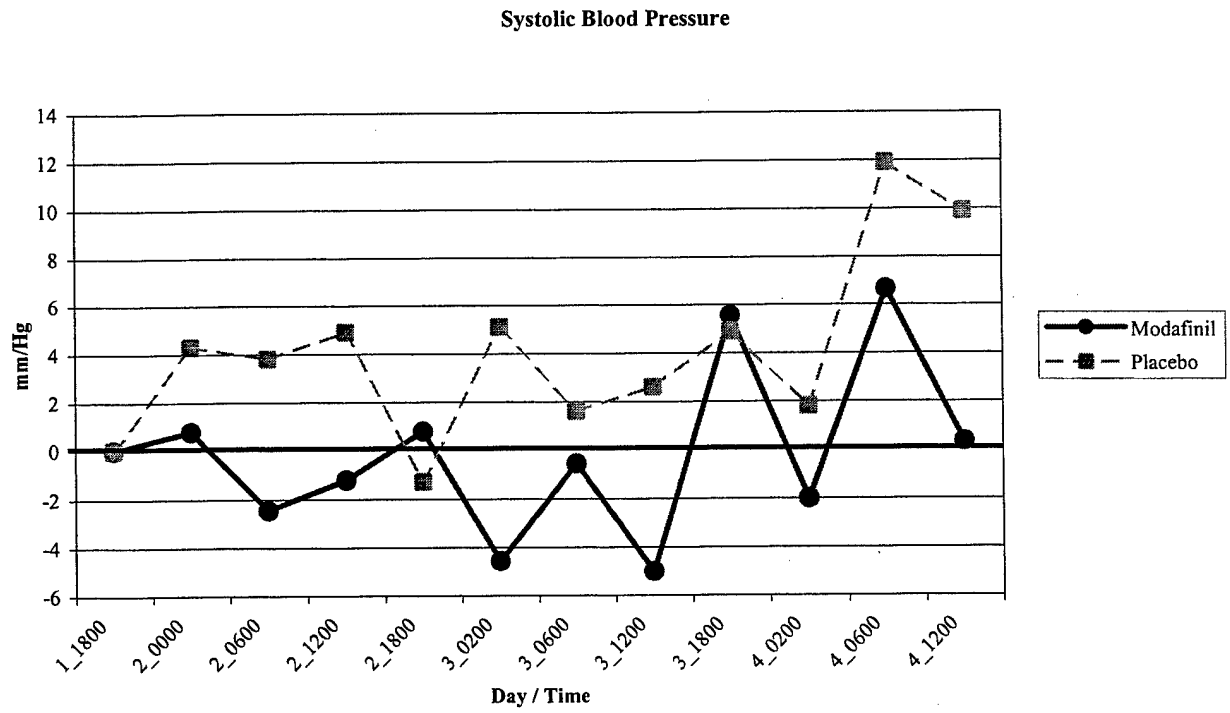


Figure 14 Systolic Blood Pressure - Changes from Baseline
Baseline values: Modafinil = 128, Placebo = 128

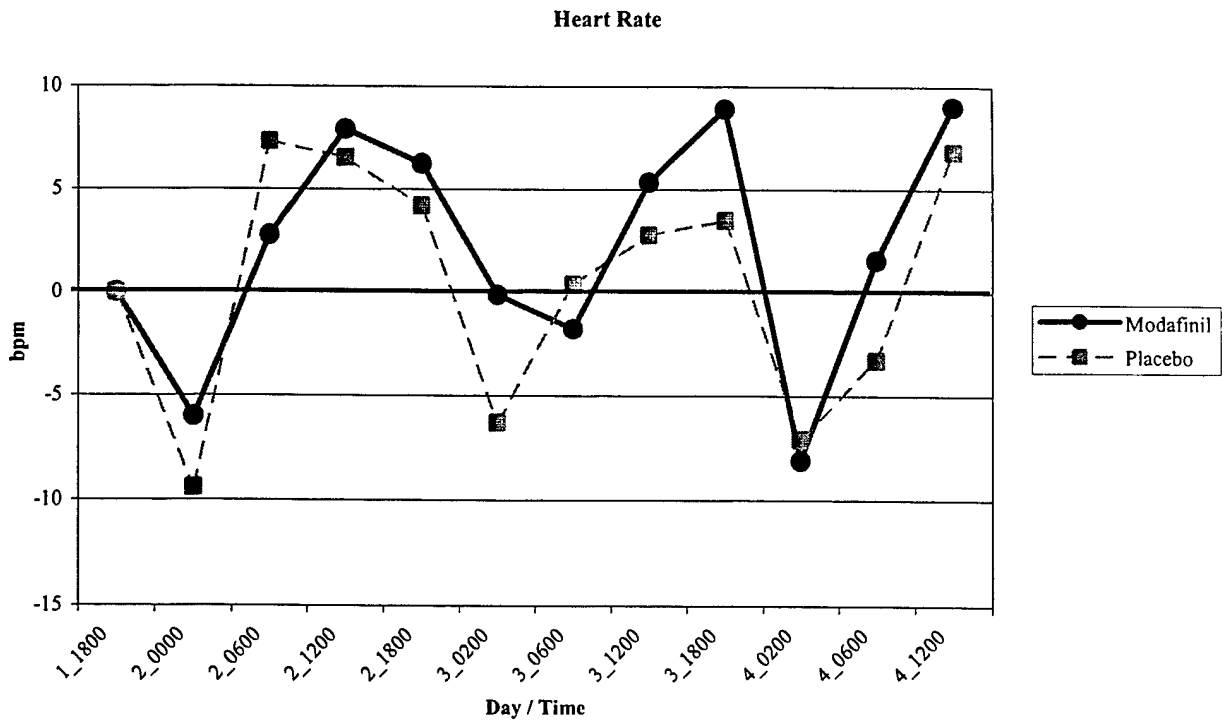


Figure 15 Heart Rate - Changes from Baseline
Baseline values: Modafinil = 70, Placebo = 68

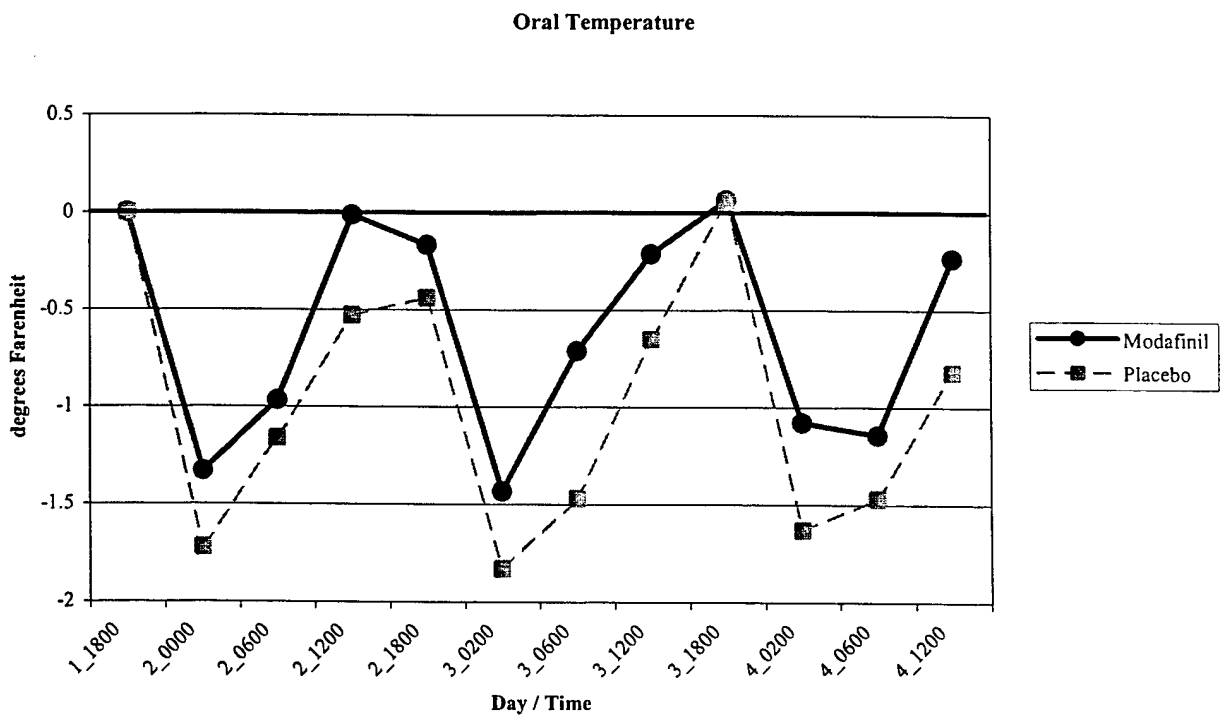


Figure 16 Oral Temperature - Changes from Baseline
Baseline values: Modafinil = 98.1, Placebo = 98.1

Jump - No significant drug effects were found for any of the outcome measures of this test. There was a main effect of time for jump height, ELF, and ground time ($p<0.001$ for each). Jump height follows a fairly strong circadian pattern for both groups, see Fig 17. ELF shows similar trends but with modafinil remaining consistently slightly higher than placebo, see Fig 18. Ground time also shows circadian variation with modafinil generally remaining lower than placebo, see Fig 19.

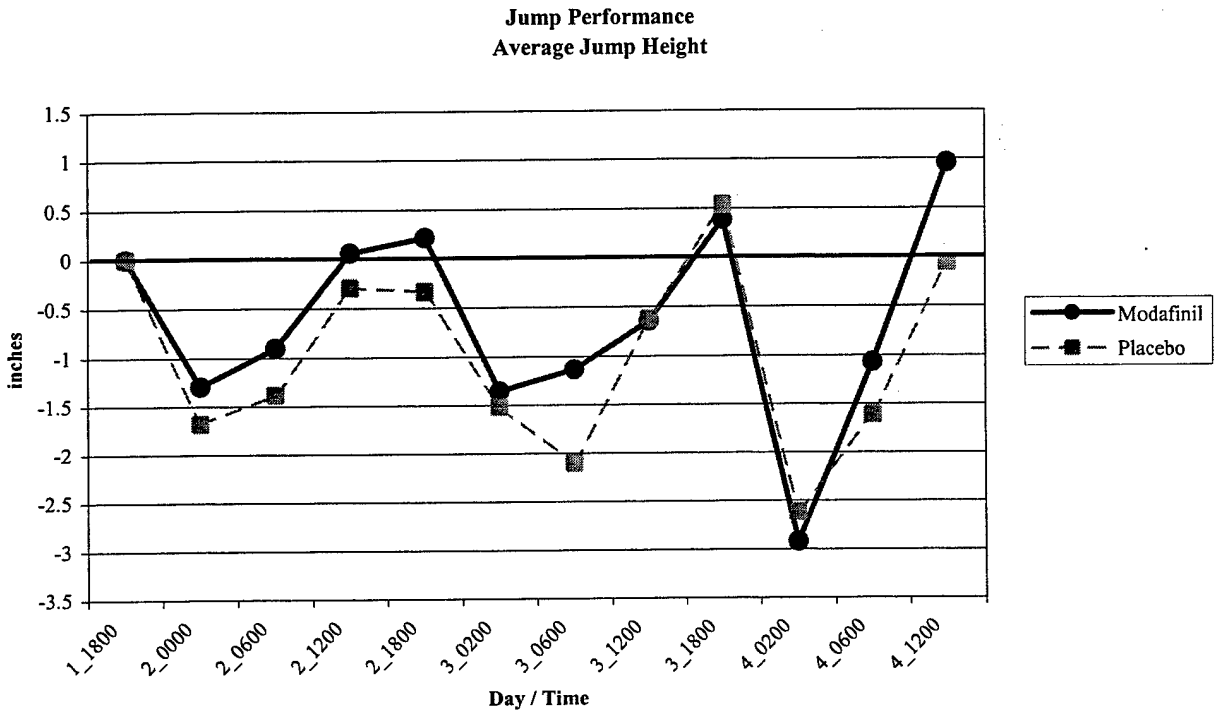


Figure 17 Jump Task - Jump Height Changes from Baseline
Baseline values: Modafinil = 16.3, Placebo = 15.0

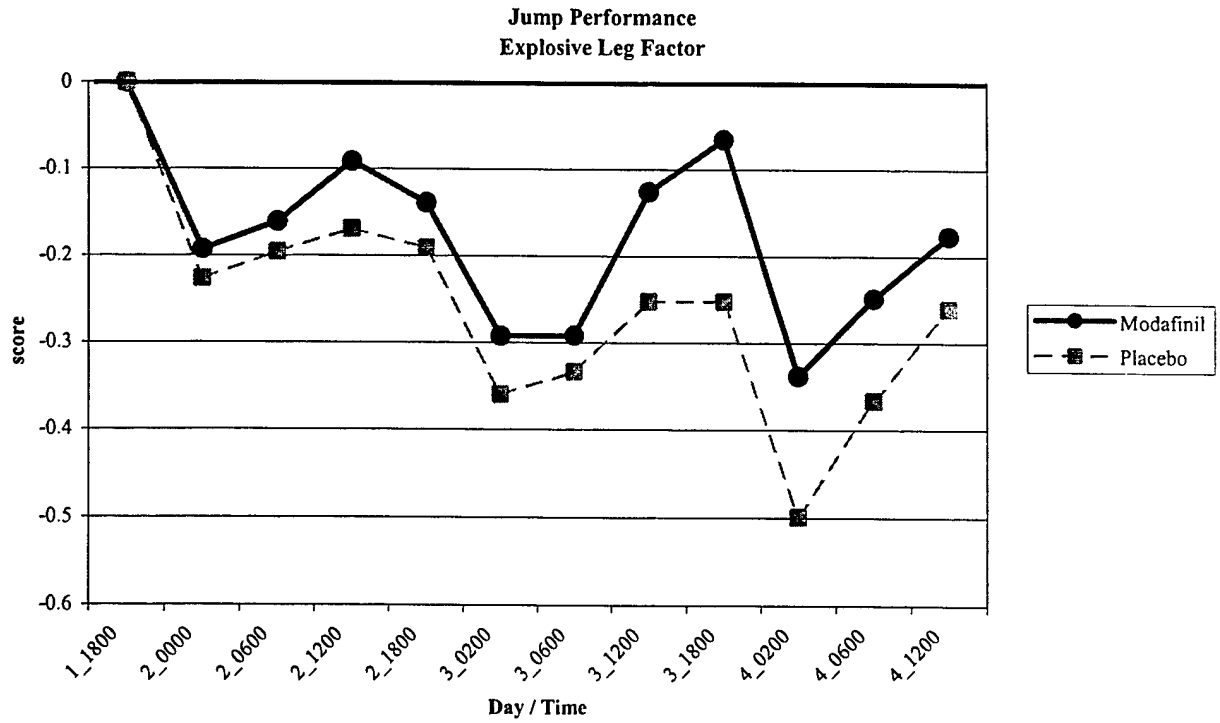


Figure 18 Jump Task - Explosive Leg Factor Changes from Baseline
Baseline values: Modafinil = 1.29, Placebo = 1.35

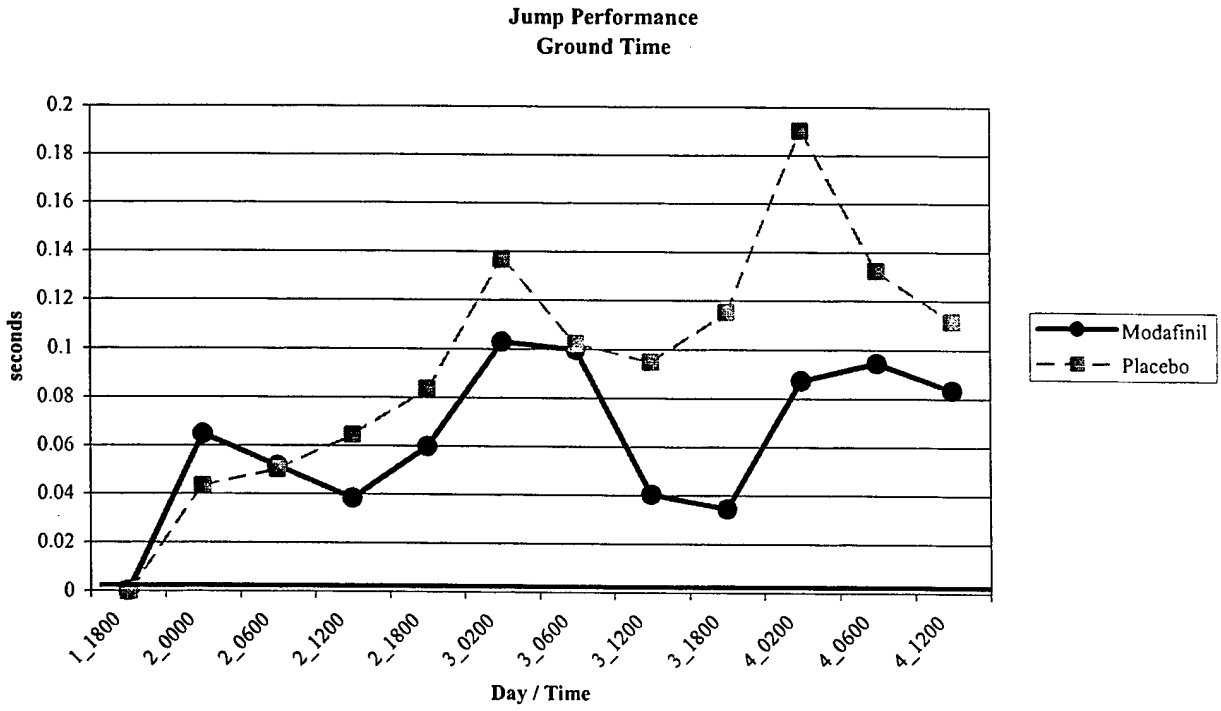


Figure 19 Jump Task - Ground Time Changes from Baseline
Baseline values: Modafinil = 0.46, Placebo = 0.45

Questionnaires- Questionnaire results are based upon 20 participants. On the modafinil use questionnaire, 100% of the participants reported that they would use modafinil in the field. These answers were based upon either their own experience with modafinil or from evaluating their partner's performance. Some reasons for this high acceptance follow (slightly paraphrased): high level of alertness; no noticeable side effects; with modafinil you could still rest, but could move if you needed; it really affects your decision-making skills (positively); allows improved function while fatigued; helps you stay more active and awake, but not hyperactive; and if I wanted to sleep I could sleep. The post-mission questionnaire returned only two reports of side effects. One participant indicated an inability to sleep, and another participant reported nausea if modafinil were taken on an empty stomach. Trek performance for nine of the ten teams was rated as superior for the modafinil member by both the modafinil user and his partner. One team rated both participants performance as equal. All of the participants guessed accurately as whether they had taken modafinil or the placebo.

**Discussion**

In general, the cognitive and sleepiness data support the hypothesis that modafinil would partially attenuate the performance decrements associated with fatigue (both sleep loss and circadian variation) in this study. The trends are fairly consistent across tests even though statistically significant differences between the conditions are intermittent. This result is not surprising when one considers that the final sample size for most of the performance test ANOVAs was seven modafinil participants and ten placebo participants. The resulting power for the post-hoc comparisons is equal to or below 0.50. Given this low power, observing a positive modafinil drug effect in 6 of 17 ARES and Sleep Scale variables supports the efficacy of modafinil in a field environment.

The impact of fatigue upon cognitive performance metrics may not have been as great in this study as has been seen in some laboratory studies. It has been noted in the fatigue literature that motivation may mask the effect of fatigue (see Kjellberg 1977 for a review). Certainly the environment in which this study was conducted was much more stimulating than the normal laboratory setting. Whereas typically a laboratory is rather sterile and the events within a study are highly routinized (i.e., the environment is dull and highly predictable), the participants in this study were hiking though attractive countryside in pleasant weather with myriad natural distractions. The participants only interacted with the research staff for about one of every six hours. During the hours and miles between checkpoints they were unmonitored and able to plan their activities according to their mood. Some participants climbed up hills to take in a view while others hunted squirrels with slingshots. It is therefore likely that fatigue was masked to a relatively greater extent in this study than the typical laboratory study. Masking does not change the performance capability of the individual merely the degree to which the underlying sleep drive is expressed. So, we are not stating that participants weren't tired, rather that the participants were more engaged, and thus performed relatively better, in this study than in laboratory studies of similar duration.

The one performance measure which graphically indicated that placebo did consistently better than modafinil was accuracy for CPT. This visual effect is probably entirely due to the fact that the modafinil group's baseline was near perfect (98.7%) whereas the placebo group was a bit lower (94.4%). Therefore the modafinil group had no "room to grow." It is likely that the placebo group, for whatever reason, was not completely trained on the task. Indeed the effect of learning is likely ubiquitous across the performance measures. Many of the modafinil group performance curves show improvements on the various tests. Thus we should regard the data as representing an optimistic view of the effect of fatigue upon performance. That is, performance

on a well-learned task would be worse than what is seen in this study. Some learning is unavoidable on these types of tasks over the time course of this study. Participants completed a total of 23 trials over the course of four days and three nights. Such spaced *testing* appears to be a near-optimal *training* schedule. Thus more training should be accomplished on future evaluations (participants completed 10 trials over three days for training). It is often the case in field research that training is accomplished days or hours prior to the initiation of data collection proper. Training literature revels that we should distribute training over a longer time period to allow for greater learning between trials. Such an approach would likely be more effective than the one employed in this study where most of the training trials were accomplished in a single sitting. Unfortunately, the training schedule in this study was a constrained due to the limited availability of the AF Survival Specialists used as participants.

The greatest performance decrements were seen in the early morning hours of the fourth day. If we examine the placebo group and compare the worst performance at any trial for each test to its baseline we see maximal throughput decrements of 12% for Four Choice, 22% for Logical Reasoning, 24% for Math, 20% for CPT, and 37% for ELF from the Jump Test. Stated another way, performance on the most sensitive cognitive test (Logical Reasoning) was observed to remain at 76% of baseline or better. This value sets the lower limit or floor of the maximum observable fatigue effect. This is somewhat of a limited performance range and reduces the opportunity for modafinil to show positive effects.

Modafinil appeared to raise DBP over the course of the study. However, it should be noted that the 1800hrs checkpoint occurred 2 hrs after a modafinil dose, the most temporally proximal of any trials to a dose time, and that there was almost no elevation in DBP compared to baseline at either 1800hr checkpoint. Given that modafinil has a t max of approximately 2 hrs, it seems odd that the time points which should be the most affected (testing for the 1800hrs checkpoint began at 1800hrs and went until about 2100hrs) by modafinil should show essentially no elevation. Overall, the highest mean elevation for DBP was about 7 mm/Hg above baseline, not a value to raise clinical concerns.

There were no significant drug differences found for oral temperature. However, Figure 16 shows some separation between the conditions and the data seem to provide evidence for temperature to be increased in the modafinil condition compared to the placebo condition. The difference in delta magnitude is quite small (about 0.4° Fahrenheit). It also appears that rather than elevate temperature generally modafinil tends to raise the temperature troughs. This effect is similar to the temperature effect seen with bright light treatment where the normal circadian temperature decrease is attenuated somewhat.

Physical performance, as measured by the jump test, tended to follow the circadian pattern. This makes particular sense when one considers that cooler muscle tends to perform less effectively than warmer muscle, and the temperature ranged from highs in the 80's to lows in the 30's over the course of the study. It also appears that fatigue increasingly impacted jump performance, particularly for the placebo condition and particularly at night.

This study was important in a couple of ways for determining the usefulness of modafinil. First it applied modafinil to a realistic field environment with a requirement for moderate physical activity. Most previous studies have applied modafinil in a laboratory environment where little physical activity was performed. Second, the participants utilized were experts in their occupation. That is, they professionally taught others how to survive and evade in enemy

territory. This population offered a great deal of relevant experience to address the research question, and their thoughts on modafinil usage were of the highest importance in this study. Therefore, one of the most significant findings was the acceptance of modafinil amongst E & E experts was overwhelmingly high, with few side effects reported and their unanimous agreement that modafinil was useful for field operations.

**Conclusions**

Modafinil provides an alertness-maintenance and relatively consistent performance advantage over placebo. Participants felt modafinil was operationally relevant and recommended its use in the field. Participants reported few side effects. Overall, it is recommended that further research be conducted on this promising alertness aid. It is also recommended that consideration be given by the USAF to incorporating modafinil into various operational domains where sleep is often not an option allowed to the warfighter.

## 11. References


Air Force Instruction 11-2, Flying Operations/Aircrew Training

Baranski, J., Cian, C., Esquivie, D., Pigeau, R., & Raphel, C. (1998). Modafinil During 64 Hr of Sleep Deprivation: Dose-Related Effects on Fatigue, Alertness, and Cognitive Performance. *Military Psychology, 10(3)*, 173-193.

Baranski, J. and Pigeau, R. (1997) Self-monitoring cognitive performance during sleep deprivation: effects of modafinil, d-amphetamine and placebo. Journal of Sleep Research, 6, 84-91.

Batéjat, D., & Lagarde D. (1999). Naps and Modafinil as Countermeasures for the Effects of Sleep Deprivation on Cognitive Performance. Aviation, Space, & Environmental Medicine, 70(5), 493-498.

Bensimon, G., Benoit, D., Lacomblez, L., & Weiler, E. (1991). Antagonism by Modafinil of the Psychomotor and Cognitive Impairment Induced by Sleep- deprivation in 12 Healthy Volunteers. European Psychiatry, 6(2), 93-97.

Buguet, A., Montemayeur, A., Pigeau, R., & Naitoh, P. (1995). Modafinil, d-amphetamine and placebo during 64 hours of sustained mental work. II. Effects on two nights of recovery sleep. Journal of Sleep Research, 4, 229-241.

Caldwell, J.A., Caldwell J.L., Smythe, N., and Hall K. (2000). A double-blind, placebo-controlled investigation of the efficacy of modafinil for sustaining the alertness and performance of avaitors: a helicopter simulator study. Psychopharmacology, 150, 272-282.

Cephalon, Inc. (1998). Provigil Prescribing Information Sheet. West Chester, PA.

Eddy, D., Gibbons, J., Storm, W., Miller, J., Cardenas, R., Stevens, K., Hickey, P., Barton, E., Beckinger, R., & Whitmore, J. (2001). The effect of modafinil upon cognitive and vestibular performance under a single night of sleep-loss. The XV$^{th}$ Annual International Conference of Night and Shiftwork. Hayama, Japan.

HQ ACC/SG Memorandum, 27 Sep 1999: Operational Use of No-Go Pills (Attach #1)

Lagarde, D., & Batejat, D. (1995). Disrupted Sleep-Wake Rhythm and Performance Advantages of Modafinil. Military Psychology, 7(3), 165-191.

Lagarde, D., Batéjat, D., Van Beers P., Sarafian D., & Pradella, S. (1995). Interest of modafinil, a new psychostimulant, during a sixty-hour sleep deprivation experiment. Fundamentals of Clinical Pharmacology, 9, 271-279.

Lin, J., Hou, Y., Rambert, F., & Jouvet, M. (1997). Awakening profiles of modafinil in sleep-deprived cats and its induction of brain c-fos expression pattern distinct from that caused by amphetamine or methylphenidate. Sleep Research, 26:23.

Morehouse, R., Broughton, R.J., Fleming, J., George, C.F.P., & Hill, J. (1997). Favourable Side Effect Profile of Modafinil. Sleep Research, 26, 120.

Pigeau R., Naitoh P., Buguet A., McCann C., Baranski J., Taylor M., Thompson M., & Mack I. (1995). Modafinil, d-amphetamine and placebo during 64 hours of sustained mental work. I. Effects on mood, fatigue, cognitive performance and body temperature. Journal of Sleep Research, 4, 212-228.

Stivalet, P., Esquivie, D., & Barraud, P. (1998). Effects of Modafinil on Attentional Processing During 60 Hours of Sleep Deprivation. Human Psychopharmacology Clinical & Experimental, 13(7), 501-507.

Wong, Y., Gorman, S., McCormick, G., & Grebow, P. (1997). Single-dose pharmacokinetics of modafinil and Methylphenidate given alone and in combination to healthy male volunteers. Sleep Research, 26, 133.

**Attachment A**
**EXPERIMENTAL SCHEDULE**

| Time | Day 1 | Day 2 | Day 3 | Day 4 |
|---|---|---|---|---|
| 0000 | Pre-Event Sleep | Checkpoint-Test-Dose | Sleep | Sleep |
| 0100 | | | | |
| 0200 | | | Checkpoint-Dose Test | Checkpoint-Dose Test |
| 0300 | | Test | | |
| 0400 | | | | |
| 0500 | | | | |
| 0600 | | Checkpoint-Test | Checkpoint-Test | Checkpoint-Test |
| 0700 | | | | |
| 0800 | | Dose | Dose | Dose |
| 0900 | | Test | Test | Test |
| 1000 | | | | |
| 1100 | | | | |
| 1200 | | Checkpoint-Test | Checkpoint-Test | Route Complete-Test |
| 1300 | | | | |
| 1400 | | | | |
| 1500 | | Test | Test | |
| 1600 | | Dose | Dose | |
| 1700 | | | | |
| 1800 | Begin Route-Test-Ops | Checkpoint-Test | Checkpoint-Test | |
| 1900 | | | | |
| 2000 | | | | |
| 2100 | Test | Test | Test | |
| 2200 | | | | |
| 2300 | | | | |

# Attachment B
## Trial Means and ANOVA Results

| Test | Variable | Drug Group | Baseline | Mean Change From Baseline At The Following Time Points | | | | | | | | | | | ANOVA Results | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | day2 0000h r | day2 0600h r | day2 1200h r | day2 1800h r | day3 0200h r | day3 0600h r | day3 1200h r | day3 1800h r | day4 0200h r | day4 0600h r | day4 1200h r | | Drug | Time | Drug X Time |
| 4 Choice | Accuracy | modaf | 100.0 | -1.1 | .0 | .0 | .0 | .0 | -1.1 | .0 | -.6 | -1.1 | -1.7 | .0 | MSE | 21.158 | 12.302 | 12.302 |
| | | | .0 | 3.0 | .0 | .0 | .0 | .0 | 2.0 | .0 | 1.6 | 2.0 | 2.1 | .0 | df | (1,15) | (5,75)[h] | (5,75)[h] |
| | | placebo | 100.0 | -.8 | -2.0 | -2.4 | -2.8 | -1.2 | -2.0 | -2.8 | -2.8 | .0 | .0 | -.4 | F | 2.324 | .581 | 1.685 |
| | | | .0 | 1.7 | 4.3 | 2.8 | 4.2 | 2.7 | 3.9 | 5.0 | 5.0 | .0 | .0 | 1.3 | p | .148 | .714 | .149 |
| | MRTC | modaf | 376.1 | 5.4 | -.6 | 6.8 | -3.0 | 7.3 | -16.4 | -11.1 | -23.7 | 29.3 | -10.1 | -.6 | MSE | 4850.3 | 766.93 | 766.93 |
| | | | 39.6 | 27.6 | 36.6 | 39.0 | 45.2 | 45.2 | 48.9 | 51.6 | 37.3 | 35.3 | 35.2 | 39.6 | df | (1,15) | (10,150) | (10,150) |
| | | placebo | 346.10 | 18.8 | 11.3 | 11.7 | 9.6 | 46.9 | 10.0 | 1.9 | 1.4 | 26.4 | 5.1 | 13.8 | F | 2.330 | 3.308 | .686 |
| | | | 27.80 | 22.2 | 19.2 | 27.7 | 26.1 | 42.2 | 32.4 | 31.3 | 21.9 | 29.2 | 26.2 | 24.5 | p | .148 | **.001** | .737 |
| | SDRTC | modaf | 69.9 | -3.3 | -6.7 | 41.4 | 8.7 | 3.1 | 10.1 | 5.3 | -7.7 | 66.7 | -.7 | 24.9 | MSE | 21300.7 | 54366.3 | 54366.3 |
| | | | 46.0 | 48.2 | 45.8 | 68.4 | 55.2 | 51.9 | 71.2 | 62.1 | 60.4 | 107.5 | 40.9 | 71.4 | df | (1,15) | (2,26)[h] | (2,26)[h] |
| | | placebo | 44.5 | 22.0 | 8.8 | 24.6 | 44.6 | 185.3 | 11.5 | 29.9 | 5.9 | 6.0 | 10.4 | 38.5 | F | 1.060 | 1.258 | 1.532 |
| | | | 22.1 | 47.7 | 12.5 | 38.7 | 122.2 | 362.9 | 35.6 | 57.9 | 28.8 | 38.1 | 14.8 | 62.8 | p | .320 | .296 | .235 |
| | Thruput | modaf | 160.6 | -3.9 | .0 | -2.3 | 2.3 | -2.3[a] | 5.6 | 5.1 | 9.4[a] | [d]-14.1 | 2.0 | .6 | MSE | 859.08 | 153.13 | 153.13 |
| | | | 16.7 | 10.5 | 13.4 | 13.1 | 16.9 | 18.6 | 21.2 | 22.0 | 15.0 | 14.4 | 16.1 | 15.0 | df | (1,15) | (10,150) | (10,150) |
| | | placebo | 173.8 | [d]-9.5 | [d]-7.5 | [c]-7.9 | [c]-8.5 | [d]-21[a] | -7.2 | -4.6 | -4.5[a] | [d]-12.3 | -2.3 | [c]-7.0 | F | 3.909 | 2.551 | .807 |
| | | | 14.1 | 9.1 | 8.6 | 11.8 | 13.7 | 18.5 | 15.2 | 17.1 | 14.5 | 13.7 | 12.7 | 10.8 | p | **.067** | **.007** | .622 |
| Logical Reasoning | Accuracy | modaf | 94.4 | 1.2 | 1.6 | 2.7 | 1.6 | -1.2 | 5.2 | 2.0 | 2.8 | .8 | .4 | 3.0 | MSE | 195.42 | 55.524 | 55.524 |
| | | | 3.6 | 6.2 | 6.0 | 6.2 | 8.0 | 9.7 | 4.4 | 2.6 | 3.2 | 8.1 | 4.4 | 3.3 | df | (1,15) | (5,82)[h] | (5,82)[h] |
| | | placebo | 94.2 | 3.1 | 2.0 | 2.5 | -.8 | -1.2 | -.8 | .6 | -.1 | -4.6 | -1.2 | -.5 | F | .847 | 1.152 | .796 |
| | | | 2.8 | 4.4 | 3.9 | 3.6 | 6.6 | 7.5 | 9.1 | 3.7 | 3.2 | 13.4 | 7.7 | 8.4 | p | .372 | .340 | .566 |
| | MRTC | modaf | 2062 | 196 | 210 | 139 | 96 | 110 | -187[b] | -161 | -239 | 383 | -42 | -127[a] | MSE | 172946 | 161361. | 161361. |
| | | | 395 | 655 | 534 | 661 | 397 | 485 | 369 | 517 | 421 | 650 | 473 | 510 | df | 8 | 3 | 3 |
| | | placebo | 1925 | -45 | 57 | 184 | 220 | 369 | [c]388[b] | 141 | -78 | [c]529 | 186 | [c]343[a] | F | (1,15) | (8,118)[h] | (8,118)[h] |
| | | | 445 | 222 | 358 | 335 | 519 | 718 | 581 | 556 | 428 | 790 | 426 | 520 | p | .796 | 2.979 | 1.859 |
| | | | | | | | | | | | | | | | | .386 | **.005** | **.074** |
| | SDRTC | modaf | 894 | 45 | 40 | 7 | -20 | 43 | -144[b] | -173 | -106 | 389 | 61 | -67 | MSE | 153374 | 142662. | 142662. |
| | | | 263 | 563 | 359 | 464 | 257 | 349 | 291 | 274 | 296 | 760 | 518 | 242 | df | 6 | 0 | 0 |
| | | placebo | 853 | [c]-183 | -165 | 133 | 78 | 105 | 328[b] | 110 | -94 | [c]447 | 70 | 263 | F | (1,15) | (7,109)[h] | (7,109)[h] |
| | | | 374 | 313 | 350 | 453 | 554 | 545 | 596 | 565 | 424 | 749 | 463 | 534 | p | .254 | 3.138 | 1.770 |
| | | | | | | | | | | | | | | | | .622 | **.004** | **.098** |
| | Thruput | modaf | 27.9 | -.9 | -2.3 | -.4 | -.7 | -1.9 | [c]4.4[b] | 3.3 | 4.1 | -4.9 | 1.0 | 3.4[b] | MSE | 299.69 | 23.200 | 23.200 |
| | | | 6.9 | 6.7 | 7.0 | 8.8 | 4.8 | 8.0 | 5.4 | 6.9 | 6.3 | 9.9 | 7.4 | 5.8 | df | (1,15) | (10,150) | (10,150) |
| | | placebo | 29.8 | 1.8 | .3 | -1.0 | -1.6 | -3.6 | [c]-4.3[b] | -.7 | 2.9 | [c]-6.5 | -2.4 | -3.8[b] | F | .728 | 3.772 | 2.207 |
| | | | 8.3 | 4.0 | 6.2 | 4.9 | 5.4 | 9.1 | 7.0 | 7.3 | 6.0 | 9.9 | 6.2 | 6.7 | p | .407 | **<.001** | **.020** |

| Test | Variable | Drug Group | Baseline | Mean Change From Baseline At The Following Time Points | | | | | | | | | | | ANOVA Results | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | day2 0000hr | day2 0600hr | day2 1200hr | day2 1800hr | day3 0200hr | day3 0600hr | day3 1200hr | day3 1800hr | day4 0200hr | day4 0600hr | day4 1200hr | | Drug | Time | Drug X Time |
| Math | Accuracy | modaf | 94.4 | -1.1 | 1.5 | -.1 | -1.7 | -.4 | -.5 | 3.9 | 1.9 | -5.7 | -2.2 | -.8 | MSE | 330.4 | 119.115 | 119.115 |
| | | | 5.3 | 2.9 | 2.9 | 2.7 | 8.1 | 4.8 | 3.9 | 5.0 | 3.5 | 13.3 | 7.7 | 7.1 | df | (1,15) | (5,71)[h] | (5,71)[h] |
| | | placebo | 90.7 | 1.9 | 3.7 | .6 | -1.1 | 1.1 | -3.8 | 1.5 | -1.3 | -5.8 | -2.2 | 2.5 | F | .007 | 1.675 | .397 |
| | | | 6.7 | 5.6 | 5.7 | 7.8 | 10.1 | 8.5 | 10.5 | 7.6 | 19.1 | 12.1 | 14.2 | 3.5 | p | .936 | .155 | .840 |
| | MRTC | modaf | 2191 | -40[a] | 18 | -72 | -167[b] | -95 | -126 | -230[b] | [d]-319 | -211 | [c]-334 | [c]-287[a] | MSE | 937031.2 | 95327.9 | 95327.9 |
| | | | 643 | 236 | 240 | 280 | 290 | 310 | 295 | 315 | 312 | 697 | 390 | 358 | df | (1,15) | (7,106)[h] | (7,106)[h] |
| | | placebo | 1881 | [d]180[a] | [d]221 | 173 | [d]231[b] | 97 | 179 | 154[b] | -78 | 87 | -123 | 66[a] | F | 3.714 | 2.992 | .341 |
| | | | 494 | 247 | 303 | 337 | 258 | 414 | 494 | 386 | 507 | 408 | 512 | 392 | p | **.073** | **.006** | .934 |
| | SDRTC | modaf | 676 | -52 | 115 | 48 | -100 | -4 | 24 | -47 | -25 | 87 | -24 | -2 | MSE | 216738.0 | 33302.3 | 33302.3 |
| | | | 173 | 204 | 152 | 201 | 214 | 209 | 170 | 169 | 212 | 330 | 159 | 241 | df | (1,15) | (6,91)[h] | (6,91)[h] |
| | | placebo | 670 | -34 | 2 | -24 | 11 | 77 | 24 | 14 | -24 | 194 | 49 | 60 | F | .186 | 2.273 | 1.058 |
| | | | 224 | 155 | 217 | 107 | 85 | 129 | 136 | 111 | 180 | 295 | 221 | 256 | p | .672 | **.043** | .394 |
| | Thruput | modaf | 26.6 | -.3 | -1.4 | .4 | .6 | 1.1 | 1.0 | 4.3 | 4.9 | -1.4 | 3.1 | 4.0 | MSE | 315.432 | 27.662 | 27.662 |
| | | | 9.0 | 4.1 | 5.2 | 4.6 | 7.0 | 6.8 | 3.4 | 5.6 | 4.9 | 13.9 | 6.2 | 6.0 | df | (1,15) | (7,98)[h] | (7,98)[h] |
| | | placebo | 30.0 | -2.1 | -2.6 | -1.9 | -4.1 | -1.9 | -3.4 | -1.6 | .8 | -7.1 | .3 | -.1 | F | 1.895 | 4.025 | .526 |
| | | | 10.3 | 4.7 | 6.4 | 5.7 | 4.5 | 5.3 | 8.0 | 5.8 | 7.1 | 9.9 | 7.7 | 7.0 | p | .189 | **.001** | .802 |
| CPT | Accuracy | modaf | 98.7 | -.2 | -1.3 | -1.1 | -1.4 | -.6 | -1.8 | -1.7 | -1.7 | -2.2 | -2.2 | -2.8 | MSE | 144.745 | 8.494 | 8.494 |
| | | | 1.5 | 2.1 | 3.1 | 2.3 | 1.9 | 2.0 | 3.8 | 2.3 | 4.5 | 4.0 | 2.1 | 2.7 | df | (1,15) | (10,150) | (10,150) |
| | | placebo | 94.4 | 1.1 | 1.9 | 3.1 | -.0 | .8 | -.5 | -1.0 | -.8 | -1.6 | -.9 | -.5 | F | .900 | 1.865 | .586 |
| | | | 5.2 | 4.4 | 5.0 | 4.9 | 6.2 | 4.9 | 6.6 | 5.3 | 4.8 | 3.6 | 6.5 | 6.3 | p | .358 | **.054** | .824 |
| | MRTC | modaf | 478.9 | 1.7 | .0 | -21.0 | -38.4 | -18.1 | -24.3 | -42.9 | -38.1 | .7 | -21.9 | -38.6 | MSE | 23538.7 | 944.5 | 944.5 |
| | | | 54.8 | 40.4 | 58.9 | 49.5 | 52.5 | 45.6 | 41.4 | 43.3 | 64.2 | 58.2 | 52.8 | 59.4 | df | (1,15) | (10,150) | (10,150 |
| | | placebo | 425.6 | 22.2 | 29.7 | 9.4 | 9.4 | 26.6 | 30.2 | -2. 1 | -29.9 | 52.5 | 32.9 | -4.6 | F | 2.766 | 5.943 | .971 |
| | | | 54.9 | 55.3 | 56.7 | 51.7 | 52.3 | 60.9 | 73.2 | 43.2 | 41.8 | 57.5 | 68.2 | 52.9 | p | .117 | **<.001** | .471 |
| | SDRTC | modaf | 115.9 | 9.0 | 7.6 | 3.8 | -2.6 | 9.4 | .3 | -.9 | 7.1 | 14.6 | 5.9 | .5 | MSE | 5211.5 | 373.9 | 373.9 |
| | | | 26.9 | 32.4 | 27.6 | 22.3 | 35.8 | 21.3 | 33.0 | 20.2 | 28.2 | 37.6 | 26.3 | 36.0 | df | (1,15) | (10,150) | (10,150) |
| | | placebo | 95.6 | 11.4 | 16.4 | 11.0 | 8.2 | 9.2 | 15.3 | 10.1 | 11.2 | 16.2 | 21.2 | 16.3 | F | .605 | .588 | .370 |
| | | | 24.1 | 29.7 | 27.7 | 25.9 | 17.7 | 31.9 | 34.0 | 27.3 | 23.0 | 29.4 | 30.3 | 23.8 | p | .449 | .822 | .958 |
| | Thruput | modaf | 110.29 | -2.43 | -7.43 | 1.96 | 2.00 | -.29 | .43 | 7.43 | 3.57 | -9.43 | -.14 | 7.64 | MSE | 2790.8 | 355.5[h] | 355.5[h] |
| | | | 36.43 | 11.28 | 23.50 | 10.77 | 19.16 | 14.58 | 8.32 | 13.45 | 29.63 | 37.22 | 21.60 | 20.64 | df | (1,15) | (5,75) | (5,75) |
| | | placebo | 114.70 | -2.50 | -5.00 | 1.80 | .44 | -6.73 | -5.30 | .58 | 5.43 | -22.8 | -7.40 | 1.80 | F | .248 | 3.454 | .538 |
| | | | 42.43 | 17.58 | 13.94 | 15.70 | 16.03 | 23.33 | 22.60 | 14.46 | 15.28 | 29.31 | 23.02 | 22.69 | p | .626 | **.007** | .746 |
| Sleep Scale | Score | modaf | 1.9 | [c].4 | [d]2.0 | [c]1.0 | 6 | [d]1.9 | [d].7[a] | .4 | .1 | [d]1.3 | 1.3 | -.3[b] | MSE | 9.972 | 1.080 | 1.080 |
| | | | .9 | .5 | 1.5 | 1.2 | 1.0 | 1.2 | .8 | 1.3 | 1.1 | 1.3 | 2.1 | 1.0 | df | (1,15) | (8,116)[h] | (8,116)[h] |
| | | placebo | 1.7 | .1 | [d]1.0 | [c].8 | [d]1.3 | [d]1.4 | [d]1.7[a] | [d]1.1 | [d]1.0 | [d]2.3 | [d]1.8 | [d]1.3[b] | F | .717 | 5.176 | 3.027 |
| | | | .5 | .9 | .9 | 1.3 | 1.6 | 1.4 | 1.2 | 1.3 | 1.1 | 1.6 | 1.6 | 1.5 | p | .410 | **<.001** | **.004** |

| Test | Variable | Drug Group | Baseline | Mean Change From Baseline At The Following Time Points | | | | | | | | | | | ANOVA Results | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | day2 0000hr | day2 0600hr | day2 1200hr | day2 1800hr | day3 0200hr | day3 0600hr | day3 1200hr | day3 1800hr | day4 0200hr | day4 0600hr | day4 1200hr | | Drug | Time | Drug X Time |
| Jump Test | Height | modaf | 16.26 | -1.30 | -.90 | .06 | .21 | -1.36 | -1.14 | -.64 | .39 | -2.92 | -1.07 | .96 | MSE | 30.934 | 2.064 | 2.064 |
| | | | 2.25 | .94 | 1.25 | 1.13 | 1.60 | 1.77 | 2.20 | 2.60 | 1.76 | 2.66 | 1.65 | 1.45 | df | (1,17) | (6,98)[h] | (6,98)[h] |
| | | placebo | 15.04 | -1.68 | -1.39 | -.29 | -.34 | -1.52 | -2.11 | -.63 | .54 | -2.62 | -1.61 | -.06 | F | .222 | 15.953 | .707 |
| | | | 3.12 | 1.48 | 1.76 | 1.54 | 1.60 | 1.69 | 2.40 | 2.34 | 2.26 | 2.72 | 2.51 | 2.39 | p | .643 | **<.001** | .638 |
| | ELF | modaf | 1.292 | -.193 | -.161 | -.092 | -.139 | -.293 | -.292 | -.126 | -.066 | -.338 | -.249 | -.177 | MSE | .504 | .035 | .035 |
| | | | .316 | .308 | .177 | .199 | .300 | .316 | .355 | .250 | .163 | .282 | .279 | .312 | df | (1,17) | (5,85)[h] | (5,85)[h] |
| | | placebo | 1.350 | -.227 | -.196 | -.169 | -.191 | -.360 | -.334 | -.253 | -.25 | -.499 | -.367 | -.261 | F | .826 | 8.625 | .722 |
| | | | .474 | .173 | .131 | .162 | .153 | .230 | .280 | .207 | .242 | .311 | .269 | .238 | p | .376 | **<.001** | .609 |
| | Ground | modaf | .463 | .065 | .052 | .038 | .060 | .103 | .100 | .040 | .034 | .087 | .094 | .083 | MSE | .0667 | .00572 | .00572 |
| | | | .112 | .098 | .043 | .034 | .072 | .065 | .092 | .057 | .039 | .082 | .061 | .100 | df | (1,17) | (6,105)[h] | (6,105)[h] |
| | | placebo | .447 | .043 | .050 | .064 | .084 | .137 | .102 | .095 | .115 | .190 | .132 | .111 | F | .874 | 4.896 | 1.728 |
| | | | .116 | .062 | .070 | .106 | .094 | .131 | .130 | .107 | .116 | .142 | .133 | .132 | p | .363 | **<.001** | .119 |
| Vitals | HR | modaf | 70.4 | -6.0 | 2.8 | 7.9 | 6.2 | -.1 | -1.8 | 5.3 | 8.9 | -8.1 | 1.6 | 9.0 | MSE | 1458.516 | 104.129 | 104.129 |
| | | | 17.4 | 10.46 | 14.8 | 17.9 | 9.2 | 11.8 | 11.3 | 12.9 | 8.1 | 14.9 | 12.3 | 9.6 | df | (1,17) | (8,143)[h] | (8,143)[h] |
| | | placebo | 67.5 | -9.4 | 7.3 | 6.5 | 4.2 | -6.3 | .4 | 2.8 | 3.5 | -7.1 | -3.3 | 6.8 | F | .121 | 7.098 | .587 |
| | | | 8.3 | 7.8 | 22.6 | 18.8 | 15.8 | 16.1 | 12.5 | 20.0 | 16.0 | 14.7 | 14.1 | 15.5 | p | .732 | **<.001** | .795 |
| | DBP | modaf | 75.2 | .0 | -1.6 | 6.1[b] | .3 | [d]5.3[b] | .8[a] | 3.2[a] | .6 | 5.2 | [c]7.2 | 2.7 | MSE | 433.443 | 128.970 | 128.970 |
| | | | 5.5 | 9.0 | 5.6 | 10.4 | 9.4 | 6.9 | 6.2 | 10.1 | 8.0 | 8.7 | 9.7 | 12.1 | df | (1,17) | (5,92)[h] | (5,92)[h] |
| | | placebo | 82.7 | -3.0 | -12.3 | [c]-4.2[b] | [c]-6.3 | -1.9[b] | [c]-6.4[a] | [c]-4.5[a] | [c]-4.5 | -.7 | -.6 | -.7 | F | 5.587 | 2.350 | .406 |
| | | | 5.5 | 8.7 | 26.3 | 5.9 | 9.7 | 6.1 | 10.2 | 7.3 | 7.3 | 8.3 | 10.2 | 6.55 | p | **.030** | **.042** | .857 |
| | SBP | modaf | 128.3 | .8 | -2.4 | -1.2 | .8 | -4.6 | -.6 | -5.0 | 5.6 | -2.0 | 6.7 | .3 | MSE | 1935.447 | 77.892 | 77.892 |
| | | | 10.3 | 10.2 | 14.7 | 13.5 | 12.0 | 8.9 | 11.6 | 14.0 | 6.0 | 16.7 | 12.0 | 11.4 | df | (1,17) | (10,170) | (10,170) |
| | | placebo | 128.0 | 4.3 | 3.8 | 4.9 | -1.3 | 5.1 | 1.6 | 2.6 | 4.9 | 1.8 | 11.9 | 9.9 | F | .582 | 2.429 | .879 |
| | | | 16.2 | 11.0 | 16.9 | 14.5 | 17.9 | 25.2 | 20.0 | 18.2 | 14.4 | 25.2 | 14.5 | 17.6 | p | .456 | **.010** | .554 |
| | Temp | modaf | 98.1 | -1.3 | -1.0 | -.0 | -.2 | -1.4 | -.7 | -.2 | .1 | -1.1 | -1.1 | -.2 | MSE | 4.257 | .388 | .388 |
| | | | .6 | 1.0 | .7 | .8 | .9 | 1.3 | 1.0 | .9 | .6 | 1.0 | 1.0 | 1.1 | df | (1,17) | (10,170) | (10,170) |
| | | placebo | 98.1 | -1.7 | -1.2 | -.5 | -.4 | -1.8 | -1.5 | -.7 | .1 | -1.6 | -1.5 | -.8 | F | 1.995 | 16.516 | .515 |
| | | | .5 | 1.1 | .9 | .7 | .4 | .8 | .8 | 1.0 | .4 | .5 | 1.0 | .4 | p | .176 | **<.001** | .878 |

Notes: 1. Numbers in each cell of the table represent the mean (top) and standard deviation (bottom).

2. [h] Huynh-Feldt adjustment was made to the anova degrees of freedom.

3. Post-hoc significance test results:

[a] marginal difference between modafinil and placebo changes ($p \leq .10$)

[b] significant difference between modafinil and placebo changes ($p \leq .05$)

[c] marginal change from baseline ($p \leq .10$)

[d] significant change from baseline ($p \leq .05$)