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The Efficacy of Dexedrine® for the Sustainment of Helicopter Pilot Performance During 64 Hours of Continuous Wakefulness

By

John A. Caldwell, Jr.
Nicholas K. Smythe
Patricia A. LeDuc
Brian F. Prazinko
J. Lynn Caldwell
David N. Norman
Evelyn Skoumbourdis
Arthur Estrada
William D. Sprenger
Peggy S. Ruyak
Siobhan Hoffman

Aircrew Health and Performance Division

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Reviewed:

for
MORRIS R. LATTIMORE, JR.
Colonel, MS
Director, Aircrew Health &
Performance Division

Released for publication:

JOHN A. CALDWELL, Ph.D.
Chairman, Scientific Review
Committee

CHERRY L. GAFFNEY
Colonel, MC, SFS
Commanding

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J.A. Caldwell; N.K. Smythe, P.A. LeDuc; B.F. Prazinko; J.L. Caldwell; D.N. Norman; et. al.

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The purpose of this investigation was to establish the efficacy of Dexedrine for sustaining aviator performance despite 64-hours of extended wakefulness. Although earlier flight studies yielded favorable results with no significant side effects, they were restricted to sleep-deprivation periods of only 40 hours. Due to requirements for longer periods of sustained wakefulness, it was necessary to study the efficacy of Dexedrine for maintaining aviator performance during 3 days and 2 nights without sleep. To accomplish this, computerized evaluations of aviator flight skills were conducted at regular intervals as subjects completed standardized flights in a UH-60 helicopter simulator, both under Dexedrine and placebo. Laboratory-based assessments of cognitive, psychological, and central nervous system status were completed as well. Dexedrine (10 mg.) was given prophylactically (prior to signs of fatigue) at midnight, 0400, and 0800 on both deprivation days in one cycle, and placebo was given on both days in the other.

Results indicated simulator flight performance was maintained by Dexedrine for up to 58 hours, while performance under placebo rapidly deteriorated. The drug was most beneficial

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at 0500 and 0900 on the first deprivation day, but continued to attenuate impairments throughout 1700 on the second deprivation day (after 58 hours awake). Dexedrine likewise lessened the slowing of response times, the impairments in problem identification, and the reductions in performance capabilities which were evident in the cognitive data under placebo. The positive effects of Dexedrine were noticeable after only 22 hours of sustained wakefulness, but were most evident between 0500 and 1200 on both deprivation days (the times at which performance under placebo suffered the most). These were the same times at which the differences between Dexedrine and placebo were most apparent in the flight data. Dexedrine suppressed the increases in slow-wave EEG activity (associated with impaired alertness) which began to occur under the placebo condition after 23 hours of continuous wakefulness. The medication then attenuated a further increase in slow EEG activity that was present throughout 55 hours (and sometimes 59 hours) of deprivation. At the same time, Dexedrine (compared to placebo) clearly sustained self-perceptions of vigor, alertness, energy, and talkativeness, while reducing problems with fatigue, confusion, and sleepiness. Mood declines were observed after 20 hours without sleep under the placebo condition, and these were followed by further decrements which were most noticeable after 48 hours of continuous wakefulness. Ratings actually improved under Dexedrine at several times. Recovery sleep was slightly less restful under Dexedrine even though the last dose was 15 hours before bedtime (Dexedrine has an average half-life of 10.25 hours). Thus, at least two nights of recovery sleep should be required after Dexedrine is used to maintain alertness for 64 hours.

There were no clinically-significant side effects which caused the discontinuation of any participant; however, one subject experienced an increase in diastolic blood pressure that would have been cause for concern had it not decreased when the subject was retested in a prone position. Some aviators complained of palpitations and "jitteriness" under Dexedrine, but this did not detract from their performance. One of the subjects became very excitable and talkative under the influence of Dexedrine, but he did not become reckless or dangerous.

In summary, prophylactic Dexedrine administration substantially reduced the impact of sleep loss in the early morning hours and, for the most part, preserved performance for the remainder of the day in a 64-hour bout of continuous wakefulness. The beneficial effects of Dexedrine are most apparent during the circadian trough where performance and alertness under placebo are the worst. Thus, when proper restorative sleep is not available due to operational constraints, Dexedrine should be considered an effective countermeasure; however, it should not be used as a substitute for sleep. Proper crew rest management must remain a top priority to preserve our tactical advantage on the battlefield.

Table of contents

Page

General objective 1

Military relevance 1

Background 1

Objectives 4

Methods 4
- Subjects 4
- Apparatus 5
  - Dose preparation 5
  - Physiological data 5
  - UH-60 simulator 5
  - EEG evaluations 5
  - Desktop flight simulation task 5
  - Mood questionnaires 6
  - Vigilance/cognitive tests 6
  - Polysomnography 6

Procedure 6
- Flight performance 7
- EEG evaluations 9
- Desktop flight simulation task 10
- Mood Questionnaires (POMS and VAS) 10
- Cognitive performance evaluations 10
- Polysomnography 11
- Testing schedule 11

Data analysis 12

Results 13
- Flight performance data 13
  - Straight and levels (SLs) 13
  - Climbs 15
  - Descents 15
  - Left standard-rate turns (LSRTs) 16
  - Right standard-rate turns (RSRTs) 17
  - Left descending turn (LDT) 18
- EEG 18
  - Delta activity 19
  - Theta activity 21

Table of contents (continued)

Page

Alpha activity 24
Beta activity 27
Desktop flight simulator 28
Scores 28
Tones 28
POMS 29
Tension-anxiety scale 30
Depression-dejection scale 31
Anger-hostility scale 31
Vigor-activity scale 31
Fatigue-inertia scale 32
Confusion-bewilderment scale 33
VAS 33
MATB 36
Communications 36
Resource management 38
Systems monitoring 38
Tracking 40
Vital signs data 42
Oral temperature 42
Pulse 44
Systolic blood pressure 44
Diastolic blood pressure 44
Polysomnographic data 45

Discussion 46
Flight performance 47
MATB and desktop simulator tasks 48
Physiological indices of fatigue/alertness 48
Self-reported mood and sleepiness 49
Recovery sleep 50
Subjective observations 51

Summary and conclusions 53

Acknowledgments 54

References 54

Appendices

A. Flight manuevers 59

Table of contents (continued)

Page

B. Manufacturer's list 60

List of tables

1. Dose orders 7
2. Testing schedule 7
3. Status of the automatic trim system during each upper-airwork maneuver 8
4. Scoring bands for flight performance data 9

List of figures

1. Effects of drug and session, drug and iteration, and session on flight performance in the SLs 14
2. Effects of drug and session on the climb 15
3. Effects of the combination of drug and session and the effects of session (with the other factors collapsed) on performance of the descents 16
4. Effects of the drug and session combined and session (with the other factors collapsed) on the left standard-rate turns 17
5. Effects of drug and session combined and session (with the other factors collapsed) on the right standard-rate turns 18
6. Effects of drug and session on the left descending turn 19
7. Effects of eye closure and session and the effects of eye closure and drug on EEG delta activity 19
8. The effects of drug and session EEG delta activity at Fz, Cz, and Pz 20
9. Effects of session (with all other factors collapsed) on EEG delta activity at Fz, Cz, and Pz 21
10. The effects of drug, eye closure, and session on EEG theta activity at Cz and Pz 22
11. Effects of eye closure and session on EEG theta activity at Cz. 22
12. Effects of drug and session (with the eyes condition collapsed) on EEG theta at Fz, Cz, and Pz 23
13. Effects of session (with all other factors collapsed) on EEG theta activity at Fz, Cz, and Pz 24
14. Effects of drug, eye closure, and session on EEG alpha activity at Fz and Cz 25
15. Effects of eye closure and session on EEG alpha activity at Fz, Cz, and Pz 25
16. Effects of drug and session on alpha activity at Fz 26
17. Effects of session (with all other factors collapsed) on EEG alpha at Fz, Cz, and Pz 27
18. Effects of drug and session on beta activity at Pz, and the effects of session (with the other factors collapsed) on beta activity at Fz 28
19. Effects of drug and session, and session (with the other factors collapsed) on the number of targets missed during the desktop flight simulation task 29
20. Effects of drug and session, and session (with the other factors collapsed) on reaction times to target tones during the desktop simulation task 30

Table of contents (continued)

Page

21. Effect of session (with all other factors collapsed) on ratings of POMS tension 30
22. Effect of session (with all other factors collapsed) on POMS depression-dejection ratings 31
23. Effects of drug and session and session (with the other factors collapsed) on POMS vigor-activity ratings 32
24. Effects of drug and session, and session (with the other factors collapsed) on POMS fatigue-inertia ratings 32
25. Effects of drug and session, and session (with the other factors collapsed) on POMS confusion-bewilderment ratings 33
26. Effects of drug and session on VAS alertness, energy, irritability, sleepiness, and talkativeness 35
27. Effect of session (with the other factors collapsed) on VAS ratings. 36
28. Effect of session on reaction time for correct responses, standard deviation of reaction time, and time out errors in the MATB communications task 38
29. Effects of drug and session on reaction times to lights and dials and time outs for lights and dials on the MATB systems monitoring task 39
30. Effect of session (with the other factors collapsed) on reaction times, standard deviation of reaction times, and time out errors in the MATB systems monitoring task 40
31. Effects of drug and session, and session with the other factors collapsed on the MATB tracking task 42
32. Effects of drug and session on temperature, pulse, and blood pressure 43
33. Effect of Dexedrine and placebo on latency to sleep onset and sleep efficiency 45
34. Effects of Dexedrine and placebo on sleep architecture (minutes in each stage and percentage of each stage) 46
35. Effects of Dexedrine and placebo on the latency to REM sleep onset 46

General objective

The purpose of this investigation was to establish the efficacy of Dexedrine for sustaining aviator performance despite extended wakefulness (64 hours). Although an earlier in-flight study and two laboratory studies of Dexedrine yielded favorable results with no significant side effects, these investigations were restricted to 40 hours of continuous wakefulness. Due to requirements for longer periods of sleep deprivation, it was considered important to study the efficacy of Dexedrine in terms of maintaining aviator performance during 64 hours without sleep.

To explore the efficacy of 10-mg doses of Dexedrine for the sustainment of alertness during 3 days and 2 nights of continuous wakefulness, computerized evaluations of aviator flight skills were conducted at regular intervals as subjects completed standardized flights in a UH-60 helicopter simulator. Laboratory-based assessments of cognitive, psychological, and central nervous system status were conducted as well.

Military relevance

Current military doctrine requires that Army aviation units operate around the clock during times of conflict because success on the battlefield depends on maintaining the momentum of continuous day-night operations (Department of the Army, 1997). In part, due to the significant improvement in night fighting capability offered by night vision devices, night helicopter operations now constitute a substantial component of the modern aviation mission. Combining efficient day and night fighting capabilities across successive 24-hour periods places a significant strain on enemy resources and presents a clear tactical advantage for U.S. forces.

However, there are difficulties inherent in maintaining effective around-the-clock operations. Although aircraft can function for extended periods without adverse effects, human operators need periodic sleep for the restoration of both body and brain (Horne, 1978). Depriving humans of proper restorative sleep produces attentional lapses and slower reaction times which are associated with poor performance (Krueger, 1989).

Because it is virtually impossible for aviators to receive adequate sleep and rest during combat operations (especially in this era of personnel force reductions), it is essential that the military explore countermeasures to offset the performance decrements associated with sleep debt. Given that personnel numbers are dwindling while mission demands are expanding, pharmacological stimulants may be the only viable alternative in some situations.

Background

Around-the-clock operations are commonplace in modern society due to technological advances and industrial/economic demands. In the military, 24-hour-per-day activities often are unavoidable because of the tactical function they serve. By requiring the enemy to maintain a defensive posture throughout the day and night, enemy personnel become increasingly sleepy

and fatigued to the point of eventual incapacitation. Unfortunately, friendly forces can suffer the same fate, particularly when inadequate numbers of soldiers are available to properly staff multiple duty shifts. Krueger (1989) reports the efficiency of combatants in sustained operations can be significantly compromised by inadequate sleep. Vigilance and attention suffer, reaction time is increased, mood declines, and some personnel begin to experience perceptual disturbances. Naitoh and Kelly (1993) warn that poor sleep management in extended operations quickly leads to motivational decrements, impaired attention, short-term memory loss, carelessness, reduced physical endurance, degraded verbal communication skills, and impaired judgement. Angus and Heslegrave (1985) note that cognitive abilities suffer 30 percent reductions after only 1 night without sleep, and 60 percent reductions after a second night. Clearly, sleep loss and fatigue are major threats to unit readiness in the operational environment.

Various strategies have been investigated to minimize fatigue-related performance decrements (Babkoff and Krueger, 1992), but the combat situation remains problematic because it is intense and unpredictable. As Cornum (1994) and Angus, Pigeau, and Heslegrave (1992) have indicated, despite the desirability of maintaining alertness with adequate sleep via sleep management programs, control of the timing and duration of sleep periods often is not feasible in the operational setting. As Caldwell (1992) reported, sleep deprivation was a problem for several Army pilots during Desert Storm even though the combat period was short and commanders did their best to manage the crew rest of aviation and other personnel. It has been reported that Air Force F-15C pilots and C-141 aircrews deployed during the Gulf War also suffered significant fatigue due to inadequate rest and other factors (Cornum, 1994; Neville et al., 1994).

Because operational contraints frequently make it impossible to effectively maintain performance via sleep management, various other strategies have been explored. Unfortunately, studies of strategies based upon behavioral or environmental manipulations have not produced encouraging results. For instance, brief periods of exercise appear to be only temporarily effective for reducing the negative effects of sleep loss (LeDuc et al., 1998; Horne and Reyner, 1995a; and Angus et al., 1992). Noise and cold air seem to be either totally ineffective or, in the case of loud music, actually distracting (Horne and Reyner, 1995b). Attempts to attenuate performance and/or alertness losses by ensuring the physical fitness of sustained operations personnel likewise have proven futile (Angus et al., 1992).

At present, pharmacological countermeasures (stimulants) appear to be the only reliable method for maintaining performance during intense operational scenarios that involve significant sleep loss. Despite debate on this topic, dextroamphetamine probably is one of the best alternatives available because its actions are well understood and its effectiveness in sleep-deprived personnel has been established. Caffeine, although easy to acquire and socially acceptable, appears suitable for sustaining alertness only in relatively short (i.e, 37 hour) rather than long (i.e., 64 hour) periods of continuous wakefulness (Lagarde and Batejat, 1995). Also, while caffeine is considered by some to be preferable to amphetamine for promoting alertness in sleep-deprived individuals, others have concluded that caffeine is less-effective and more prone to produce unwanted side effects than amphetamine (Weiss and Laties, 1967). Modafinil, a new psychostimulant, may eventually prove efficacious for sustaining performance in prolonged periods of total sleep loss (Lagarde and Batejat, 1995); however, this substance is not yet

available in the United States and testing in militarily-relevant contexts is lacking. Thus, at present, it appears that amphetamines offer the greatest potential for counteracting performance decrements attributable to sustained operations.

Laboratory investigations have shown that methamphetamine substantially reduces feelings of fatigue and difficulties in spatial processing during 60 hours of work with only limited sleep (Shappell, Neri, and DeJohn, 1992). Single doses (20 mg) of dextroamphetamine have been shown to return cognitive performance to baseline levels and maintain this recovery after 48 hours of total sleep deprivation (Newhouse et al., 1989). In addition, a single 20 mg dose has been found to temporarily prevent performance decrements in subjects kept awake for approximately 34 hours (Pigeau, et al., 1995). Multiple 10-mg doses of dextroamphetamine, administered prophylactically, are known to sustain the performance of helicopter pilots throughout 40 hours of continuous wakefulness (Caldwell et al., 1995; Caldwell, Caldwell, and Crowley, 1996; and Caldwell and Caldwell, 1997a). In each of these cases, unwanted side effects were minimal (most often consisting of cardiovascular stimulatory effects rather than psychological or cognitive disturbances) and of little or no consequence in healthy young adults. Although there is a widely held view that amphetamines lead personnel to become reckless and overconfident, the studies cited above reported no indication of increased risk-taking behaviors or overestimation of performance capabilities in subjects given dextroamphetamine, a finding which has been confirmed elsewhere (Higgins et al., 1975; Baranski and Pigeau, 1997). Thus, amphetamine administration seems a logical choice for maintaining the performance of aviators who are deprived of the opportunity to sleep.

In the operational environment, it has been reported that EF-111A Raven jet crews who were administered 5 mg Dexedrine during an Air Force strike on Libya in April of 1986, were able to overcome the fatigue of the mission itself and the sleep deprivation which occurred during earlier preparation for the mission (Senechal, 1988). There were no in-flight or landing problems, and all of these aircraft returned safely to base. F-15C pilots, flying lengthy combat air patrol missions during Operation Desert Shield/Storm while suffering from sleep deprivation and circadian disruption, also benefited from the use of 5 mg tablets of dextroamphetamine on an "as needed" basis (Cornum, 1992). The medication was found to effectively sustain performance, and in fact, the unit commander ultimately concluded that dextroamphetamine administration contributed significantly to the safety of air operations. There were no reported adverse effects, even in personnel who took 10 mg at a time, and no aviators reported a need to continue the drug once proper work/sleep schedules were reinstated. This agrees with the results of a large survey of Air Force pilots (at the conclusion of the Gulf War) which indicated that dextroamphetamine was helpful in maintaining acceptable mission performance during sustained operations without inducing unwanted side effects (Emonson and Vanderbeek, 1993).

Based on the available information, well-controlled administration of dextroamphetamine appears to be an effective and safe method either for recovering the performance of sleep-deprived personnel or for preventing fatigue-related decrements in individuals who are deprived of adequate sleep due to operational constraints. The performance sustaining action of 10-mg doses of dextroamphetamine is clear, at least for relatively short periods of time (40 hours). What remains to be determined is how long dextroamphetamine can be expected to stave off the

negative consequences of sleep loss before tolerance develops or the drive for sleep overpowers the stimulant effect. The present investigation was conducted to extend our understanding of the usefulness of dextroamphetamine for maintaining performance in situations where more than 40 hours of continuous wakefulness is required.

Objectives

This investigation examined the effects of Dexedrine for safely sustaining alertness and performance of helicopter pilots despite 64 hours without sleep. The primary objective was to determine whether prophylactic and frequent amphetamine adminstration could successfully prevent the declines in mood and performance expected to result from an extended period of continuous wakefulness. The study employed a variety of assessments to determine the effects of repeated 10-mg doses of Dexedrine versus placebo on: *flight performance* measured in a UH-60 helicopter simulator, *central nervous system (CNS) function* measured by resting electroencephalograms (EEG), *psychomotor skill and attention* measured by a desktop flight simulator, *mood* measured by the Profile of Mood States (POMS) and Visual Analog Scales (VAS), *vigilance & cognitive skill* measured by the Multi-Attribute Test Battery (MATB), and *sleep architecture* measured by polysomnography.

Methods

Subjects

Five male and 1 female UH-60 qualified and current aviators were recruited to reside in the U.S. Army Aeromedical Research Laboratory (USAARL) test facility for a period of 10 days each. The mean age was 33.3 years (ranging from 27-40), the mean body weight was 173 pounds (ranging from 135 to 214), and the mean total flight time was 1245 hours (ranging from 200-2700). Aviators were individually tested on the designated tasks while remaining in the Laboratory the entire time. Subjects were required to pass a medical evaluation which included a review of medical records and a face-to-face interview with a flight surgeon prior to study enrollment. The one female was given a pregnancy test (which was negative). Exclusionary criteria were current significant illnesses of any type, past psychiatric problems, sleep disorders, or any medical condition which would have interfered with participation. None of the subjects who were screened were rejected. Subjects were not permitted to consume alcohol, caffeinated beverages, or any type of medication (other than Dexedrine, placebo, acetaminophen, or ibuprofen) for the duration of the protocol. Participants who indicated they were caffeine users during initial telephonic interviews were asked to significantly reduce or completely eliminate caffeine consumption beginning several days prior to the study, although at least two of the volunteers obviously failed to heed this advice (they both experienced headaches during the first 3 days of their participation). There was one subject who used smokeless tobacco; however, he apparently discontinued this habit during the protocol (despite being told that he would be allowed to use tobacco during the breaks between test sessions).

Apparatus

Dose preparation

Two orange gelatin capsules were administered at each dose time with approximately 8 oz. of orange juice. Each of the active capsules contained one 5-mg tablet of Dexedrine, and the placebo capsules contained only lactose powder. Ten mg doses were used because operational experience and previous investigations suggested that 5 mgs would be insufficient. Dosage levels were not adjusted according to the body weights of subjects since it is unlikely that dose titration would be performed in a field environment.

Physiological data

Oral temperatures, pulse, and blood pressure data were collected with an IVAC vital signs monitor (Model number 4200).*

UH-60 simulator

All simulator flights were conducted in a specially-instrumented UH-60 flight simulator which was equipped with a standard computer-generated visual display (set for standard daytime flight), a six-degree-of-freedom motion base, and a multi-channel data acquisition system (for analyzing various aspects of simulator control such as heading, airspeed, and altitude control). Digitized flight performance data were collected and stored on a Digital Equipment Corporation VAX computer for subsequent statistical evaluation.

EEG evaluations

The EEG evaluations conducted during each subjects' waking periods were performed with a Cadwell Spectrum 32 neurometric analyzer. This device collected 7 channels of EEG data which were stored on optical disk for subsequent analysis. For the collection of resting EEG, the low filter was set at 0.53 Hz, the high filter was set at 70 Hz, and the 60 Hz notch filter was used.

Desktop flight simulation task

The desktop flight simulation task consisted of the Microsoft Flight Simulator 4.0®, combined with a custom-designed, timed flight course (Microsoft Aircraft and Scenery Designer®). This task was run on a 486 computer with VGA graphics. Flight control was accomplished via a Virtual Pilot flight yoke (CH Products®). During each of the desktop flights, tones were presented at 8 second intervals. Forty percent were target tones (6000 Hz) which required the subject to press a response button, and 60 percent were non-targets (5000 Hz) which required no response. These tones were generated using a Coulbourne Modular Instrument system. This same system was used to tally numbers of correct responses and reaction times.

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* See manufacturers' list

Mood questionnaires

Changes in mood were assessed with the POMS (McNair, Lorr, and Droppleman, 1981) and VAS (Penetar et al., 1993). The POMS is a 65-item paper and pencil test which measures affect or mood on six scales: 1) tension-anxiety, 2) depression-dejection, 3) anger-hostility, 4) vigor-activity, 5) fatigue-inertia, and 6) confusion-bewilderment. The answers were scored by hand using scoring templates. The VAS consisted of eight 100 mm lines centered over the adjectives "alert/able to concentrate," "anxious," "energetic," "feel confident," "irritable," "jittery/nervous," "sleepy," and "talkative." At the extremes of each line, "not at all" and "extremely" were printed respectively. Subjects were asked to indicate how they felt by placing a mark along each of the lines. Scores consisted of the distance of the mark from the left end of the line (in mm).

Vigilance/Cognitive tests

Changes in basic cognitive abilities were examined with the MATB, a computer-based, aviation-related, synthetic task battery which was developed by NASA researchers (Comstock and Arnegard, 1992). The test was implemented on a 486 computer equipped with a game card (Gamecard 3, C.H. Products), a voice synthesizer card (Soundblaster 16, Creative Lab.), stereo speakers (Altec Lansing), a joystick (Advance Gravis Computer Tech. LTD), and a standard keyboard and color monitor. The test required subjects to perform a tracking task concurrent with monitoring simulated indicators of fuel levels, pump status, engine performance, and other aspects of "aircraft status." Also, subjects were required to periodically change radio frequencies as instructed via computer-generated verbal commands.

Polysomnography

Evaluations of whether subjects were experiencing sleep disturbances as a function of drug and/or long-term wakefulness were made during subjects' recovery sleep periods using a Nihon Kohden electroencephalograph (model No. EEG-4321P). The EEG data were collected using a subset of the same electrodes attached for the recording of the waking EEG (C3, C4, O1, and O2, references to contralateral mastoids, A1/A2). Four additional electrodes (SensorMedics), affixed with adhesive collars immediately prior to each sleep period, were used to collect electrooculographic (EOG) and electromyographic (EMG) data. The time constant for the EEG channels was set at 0.3, and the high filter was set at 35 Hz. For EOG (recorded from the outer canthus of each eye), the time constant was 5.0 and the high filter was set at 10 Hz. For EMG (recorded with submental electrodes), a time constant of 0.003 and a high filter setting of 120 Hz was used. The chart speed was 10 mm per second.

Procedure

Training sessions were conducted at 0900, 1300, and 1700 on Tuesday-1 following the administration of a 2.5 mg test dose of Dexedrine. Vital signs, collected between the tasks in each session, were monitored closely on this day. On Wednesday-1 (control), Saturday-1 (recovery), and Sunday-2 (control), testing sessions also began at 0900, 1300, and 1700. On Thursday-1 and Friday-1 (the first deprivation days), and on Monday-2 and Tuesday-2 (the

second sleep deprivation days), testing sessions were conducted at 0100, 0500, 0900, 1300, and 1700. On Thursday-1, Friday-1, Monday-2, and Tuesday-2, drug or placebo doses were administered. On both days of each series, doses were administered at 0000, 0400, and 0800. At each dose time, the subject received 2 orange capsules containing either 5 mg Dexedrine each (for a total of 10 mg per 2-capsule dose), or lactose. The medications/placebos were administered with 8 ounces of orange juice. The dose administration scheme was double blind and completely counterbalanced (see table 1).

Table 1.
Dose orders.

Subject number	Dose for first deprivation period	Dose for second deprivation period
1	Dexedrine	Placebo
2	Placebo	Dexedrine
3	Dexedrine	Placebo
4	Dexedrine	Placebo
5	Placebo	Dexedrine
6	Placebo	Dexedrine

A general overview of the testing schedule and dose-administration interval is presented in table 2. Note that counterbalancing was used in the actual study. Within each test period, there were several tasks presented in a standardized order. Each test session began with a 1-hour flight in the UH-60; continued with a resting EEG, the desktop simulator, the POMS and VAS; and then ended with administration of the MATB. The individual tasks are discussed below.

Table 2.
Testing schedule.

Time	Mon-1	Tue-1	Wed-1	Thu-1	Fri-1	Sat-1	Sun-2	Mon-2	Tue-2	Wed-2
		Sleep	Sleep			Sleep	Sleep			Sleep
0000		^	^	**DRUG**	**DRUG**	^	^	**PLAC**	**PLAC**	^
		^	^	Test	Test	^	^	Test	Test	^
0400		^	^	**DRUG**	**DRUG**	^	^	**PLAC**	**PLAC**	^
		^	^	Test	Test	^	^	Test	Test	^
0800		Test Dose		**DRUG**	**DRUG**			**PLAC**	**PLAC**	Disconn
		Training	Test	Test	Test	Test	Test	Test	Test	Release
1200										
		Training	Test	Test	Test	Test	Test	Test	Test	
1600										
	Start	Training	Test	Test	Test	Test	Test	Test	Test	
2000										
	Bedtime	Bedtime			Bedtime	Bedtime			Bedtime	

Flight performance

The flight evaluations required subjects to perform a variety of precision maneuvers of the type typically flown in a UH-60 (see appendix A). This flight profile consisted of four hovers followed by low-level navigation to five checkpoints and upper-airwork in which the subject was required to perform precision maneuvers based upon instrument information. Each flight concluded with a formation segment in which the subject followed a lead aircraft. For the

present report, only the results from the upper-airwork maneuvers are presented. All flights were flown under simulated daylight conditions regardless of the time of day. The maneuvers are fully described in the Aircrew Training Manual (Department of the Army, 1996).

There were a total of 15 upper-airwork maneuvers in the profile. These consisted of four straight-and-levels, two left standard-rate turns, three right standard-rate turns, two standard-rate climbs, three standard-rate descents, and one left descending turn. Some of these maneuvers were flown with the automatic trim system engaged while others were flown with the trim system off (see Table 3). During each maneuver, the subjects were required to maintain an airspeed of 120 knots, but the specific targets for other parameters such as heading, altitude, roll, slip, etc., changed depending upon which maneuver was being flown. However, subjects always attempted to maintain appropriate ideal flight parameters during each maneuver.

Table 3.
Status of the automatic trim system during each upper-airwork maneuver.

Maneuver	AFCS On/Off
Straight and level number 1	On
Left standard-rate turn number 1	On
Straight and level number 2	On
Climb number 1	On
Right standard-rate turn number 1	On
Straight and level number 3	On
Right standard-rate turn number 2	On
Climb number 2	On
Descent number 1	Off
Left descending turn	Off
Descent number 2	Off
Left standard-rate turn number 2	Off
Straight and level number 4	Off
Right standard-rate turn number 3	Off
Descent number 3	Off

The flight lasted approximately 1 hour. Each flight was coordinated and controlled by one of two console operators who instructed the subjects through the standardized maneuvers in a uniform fashion (in fact, the flights of five of the six volunteers were conducted by the same operator). Console operators ensured that subjects were flying correct headings, altitudes, airspeeds, etc., prior to marking the beginning of each maneuver to minimize problems with large offset errors attributable to improper setup. Console operators attempted to maintain a quiet environment in the cockpit throughout each flight; however, they did respond to subjects' attempts to converse and occasionally initiated conversation in order to maintain the motivation and alertness of volunteers. In the few instances where subjects fell asleep (or became drowsy to the point of total inattention) during the execution of a flight maneuver, the console operator would awaken the volunteer at the conclusion of the maneuver's allotted time or when a determination was made that the maneuver would not be completed without operator

intervention. For instance, if the maneuver called for a climb from 2000 feet to 2500 feet, but instead the subject leveled off at 2300 feet because of sleepiness, the console operator would remind the subject of the target altitude once it was apparent that the subject would not complete the maneuver independently.

Based upon the data collected between the start and stop markers throughout the flight profile, the computer calculated flight scores ranging from 0-100 (with 100 reflecting near perfect accuracy) for a variety of measures within each of the maneuvers. These scores, based upon the extent to which subjects deviated from target values, expressed how well subjects maintained specific headings, altitudes, airspeeds, and other parameters. The scoring bands for each parameter are depicted in table 4. Individual parameter scores for each maneuver were then averaged together to produce one composite flight score for each iteration of each maneuver, and these composite scores were analyzed.

Table 4.
Scoring bands for flight performance data.

	Maximum deviations for scores of:					
Measure (units)	100.0	80.0	60.0	40.0	20.0	0
Heading (degrees)	1.0	2.0	4.0	8.0	16.0 >	16.0
Altitude (feet)	8.8	17.5	35.0	70.0	140.0 >	140.0
Airspeed (knots)	1.3	2.5	5.0	10.0	20.0 >	20.0
Slip (ball widths)	0.0	0.1	0.2	0.4	0.8 >	0.8
Roll (degrees)	0.8	1.5	3.0	6.0	12.0 >	12.0
Vertical Speed (feet/m)	10.0	20.0	40.0	80.0	160.0 >	160.0
Turn Rate (degrees/s)	0.3	0.5	1.0	2.0	4.0 >	4.0

EEG evaluations

Each EEG session lasted approximately 20 minutes and began with a check to ensure electrode impedances were 5000 Ohms or less. Any impedance problems were corrected by rotating a blunted needle gently inside of the problem electrode until an adequate signal was obtained. The subjects then were instructed to relax and focus on a fixation point for 1.5 minutes during which data were collected with eyes open. This was followed by 1.5 minutes of eyes closed. There were three complete iterations of this procedure (eyes open followed by eyes closed) during each test session. Data were recorded from Fz, C3, Cz, C4, Pz, O1, and O2 referenced to linked mastoids (A1 and A2).

The EEGs for eyes-open and eyes-closed were visually scanned for three relatively artifact-free 2.5-second epochs (per eyes-open and eyes-closed iteration) on which absolute power values were calculated for each of four bands. The results were averaged to produce one set of power values for each electrode site under eyes closed and eyes open. The activity bands were defined as follows: delta (1.0-3.5 Hz), theta (3.5-8.0 Hz), alpha (8.0-13.0 Hz), and beta (13.0-20.0 Hz).

Desktop flight simulation task

Following the EEG, subjects completed a 30-minute session on the desktop flight simulator. This task required subjects to fly a timed course consisting of 21 "gates" positioned at various altitudes and headings. The first 15 gates were flown under nonturbulent conditions, while gates 16-21 were made more difficult by the addition of 20-knot winds emanating from various directions. While subjects were flying the desktop simulator, they were presented with high and low tones at 8-second intervals. The high tones required subjects to press a button located on the control yoke. The low tones required no response.

This task produced a summary score at the conclusion of each "flight." The score was calculated automatically from the elapsed time it took to fly the course, the number of gates missed, and the precision with which the subjects flew through each of the gates. The reaction times to tones were automatically printed from a solid-state modular programming system (and averages for each session were calculated via a computer spreadsheet).

Mood Questionnaires (POMS and VAS)

The POMS was given shortly after each desktop flight simulation test. Subjects were presented with a series of 65 words which described mood states, and for each "mood state," the subject indicated on a standardized answer sheet how well it described the way he/she was presently feeling. This test took approximately 5 minutes to administer and yielded scores on the six factors mentioned previously. The VAS was given after the POMS. Subjects were presented with eight adjective/descriptors and asked to indicate how each represents how they were currently feeling. This test took approximately 2 minutes to administer and yielded scores on the scales described earlier.

Cognitive performance evaluations

Following the POMS and VAS, subjects completed a 30-minute session on the MATB. The MATB included a resource (fuel) management task, a communications task, a systems monitoring task, and an unstable tracking task, each of which was presented in a separate quadrant of the computer screen. Subjects were instructed to perform the tracking task while simultaneously monitoring system status and communication channels and managing fuel resources. Subjects were not told that any one task was more or less important than another, nor were they advised about how they should divide their attention among the different subtasks.

The communications task required subjects to respond only to the call sign "NGT504" (presented over the speakers) and to make the instructed frequency change on a simulated Navigation and/or Communication radio. The *Up* and *Down* arrow keys on the keyboard were used to move from "NAV1" through "COM2," and the *Left* and *Right* arrow keys were used to change frequency. The *Enter* key was pressed to acknowledge a completed frequency adjustment. The resource (fuel) management task required subjects to maintain tanks A and B at 2500 units each (indicated by numbers below the tanks and by a tick mark in the shaded bar on the sides of the two tanks). This was accomplished by turning on or off any of the pumps labeled

1 through 8. Fuel was transferred into the tanks by activating or deactivating pumps using corresponding number keys. Periodically, a pump failure occurred and the pump turned red, but subjects were taught to correct this problem by pressing control/K. The system monitoring task required that subjects attend to four gauges (dials) marked F1, F2, F3, and F4; and two boxes (lights) marked F5 (usually green) and F6 (usually blank) on the computer screen. Subjects were to press *F5* if the F5 box was no longer green and the *F6* key if the F6 box turned red. They were to press the corresponding *F* key whenever one of the pointers in the dials deviated more than two minor or one major tick mark(s) above or below the mid-line. The tracking task required subjects to use the joystick to keep a target in the center of its window within the dotted lines that formed a rectangle.

In the resource (fuel) management task, either pump 2 or 4 failed once every 2 minutes. In the systems-monitoring task, there was either a dial or light indication requiring a response from the subject three times per minute. In the communications task, radio messages were delivered at a rate of two messages per minute. A response was required for half of these messages.

Polysomnography

The sleep recordings were made on non-deprivation nights while the aviator was sleeping in a darkened, private bedroom. Each night on which sleep was allowed, EOG and EMG electrodes were placed, and the subject was escorted into his/her bedroom at the proper time. Then the electrodes were plugged in and the signal quality was checked. Afterwards, the lights were turned out and the subject was permitted to sleep for 8 hours while electrophysiological data were recorded. There were four nights during which polysomnographic data were collected. The first was a baseline night that occurred on Tuesday-1 (following a Monday-1 adaptation night). The second and third were the recovery nights on Friday-1 and Saturday-1, and the fourth was the recovery night on Tuesday-2. Data from each of these nights were recorded on a standard paper trace for analysis according to the rules set forth by Rechtschaffen and Kales (1968). The number of minutes from lights out to the appearance of stage 2 sleep (sleep onset), the number of minutes from lights out to the first 2 minutes of REM sleep (REM latency), the percentage of time subjects spent in stages 1-4 and REM sleep, the minutes of movement, and the percentage of time subjects were awake during the night were calculated.

Testing schedule

The subject reported to the Laboratory on Monday-1 for medical examination, EEG electrode attachment, and an adaptation sleep period. On Tuesday-1, the aviator received a 2.5-mg test dose of Dexedrine, and while he/she was being periodically monitored, he/she completed three training flights in the UH-60 simulator, each of which was followed by EEG, performance, mood, and MATB testing. Afterwards, he/she retired for the day (at 2300). On Wednesday-1, there were three more test sessions which served as baseline (UH-60 simulator flights, EEG, performance, mood, and MATB), but the aviator was not allowed to go to sleep in the evening. Instead, he/she was given his/her first drug/placebo dose at 0000 hours and subsequent doses were given at 0400, and 0800 on Thursday-1. On Thursday-1, test sessions began with a flight 1 hour after each drug/placebo administration (for the first three sessions) and there were two

additional non-drug sessions as well, for a total of five equally-spaced test sessions (beginning at 0100, 0500, 0900, 1300, and 1700). The aviator repeated this test schedule on Friday-1 during which Dexedrine/placebo was given at 0000, 0400, and 0800 (this scheme--last dose at 0800--was used to avoid drug effects interfering with recovery sleep on Friday night). Subjects were continuously monitored during each deprivation period to ensure that no sleep episodes occurred. At the end of the day on Friday-1, the aviator retired at 2300 and his/her sleep was recorded. On Saturday-1, subjects were awakened at 0700, after which he/she again completed test sessions at 0900, 1300, and 1700. The second night of recovery sleep began at 2300. Upon awakening at 0700 on Sunday-2, subjects began the next 64-hour deprivation period. During this day, the aviator repeated the same schedule which was used on Wednesday-1 when there were three test sessions during the day and no sleep was allowed at night. He/she was given the first dose in his/her second series of drug/placebo doses at 0000 (midnight). On Monday-2, the subject repeated the Thursday-1 schedule, beginning with his/her first flight at 0100 and continuing through test sessions at 0500, 0900, 1300, and 1700 (with drug/placebo doses preceding the first three sessions). There was no sleep on the night of Monday-2. Instead, subjects were again tested at 0100, 0500, 0900, 1300, and 1700 on Tuesday-2, and Dexedrine/placebo was again given prior to the first three sessions (as was the case previously). Eight hours recovery sleep was permitted on the night of Tuesday-2 at 2300. On Wednesday-2, the aviator was awakened at 0700, evaluated, and released.

Data analysis

The data were analyzed with BMDP4V repeated measures analysis of variance (ANOVA). Huynh-Feldt adjusted degrees of freedom were used to correct for violations of the compound symmetry assumption where appropriate. Significant interactions (those with p values less than or equal to 0.055) were analyzed using analysis of simple effects. In cases where drug-by-session interactions were found, analysis of simple effects was used only to pinpoint differences between the two drug conditions at each level of the session factor (tests for differences across sessions at each level of the drug factor were not conducted for the reason described below). In cases where analysis of simple effects pinpointed differences across factors consisting of more than two levels (except for the session factor), multiple pairwise comparisons (posthoc tests) were performed using the F-test (contrast) procedure in BMDP4V. Significant main effects also were examined with pairwise contrasts (except for session main effects). This exception was based on the fact that there are at least 13 levels of the session factor (for POMS and VAS there were 16 levels), and conducting all possible pairwise contrasts would have substantially inflated the chances of making a Type I error. Instead, session main effects were followed up with tests for linear, quadratic, and cubic trends using the contrast procedure in BMDP4V. Although the interpretation of main effects is ill-advised when there are higher-order interactions (Kirk, 1968), they are presented in this report for the sake of completeness. However, the reader should exercise caution when interpreting such effects.

All data were analyzed for the presence of significant order effects (i.e., Dexedrine first versus placebo first) by including **order** as a between-subjects factor in each of the ANOVAs

described below. However, the small number of drug-by-order or drug-by-session-by-order interactions suggested that order effects were not a problem in this study.

All ANOVAs, except the polysomnography, consisted of at least the 2 within-subjects factors of **drug** (Dexedrine, placebo) and **session** (3 baseline/control sessions, 5 sessions from the first deprivation day, and 5 sessions from the second deprivation day, for a total of 13). This was the case for the mood, cognitive, and vital-signs data. The flight performance analyses included an additional factor called **iteration** for maneuvers which were flown multiple times during each flight profile (i.e., there were four straight-and-levels, two climbs, three descents, etc.).

For the sleep data, the analysis was a one-way ANOVA. This tested for differences across **nights** (baseline, Dexedrine recovery, placebo recovery).

Prior to analysis, the data were examined for completeness, and any missing data were estimated with BMDPAM (one of the control-day flights was missing due to a simulator malfunction, one of the MATB tests was missing due to a power failure, and several of the EEG values were set to missing due to recording artifacts in some volunteers). Generally, however, the percentage of missing data was small.

Results

Flight performance data

The flight performance scores from 3 baseline flights (at 0900, 1300, and 1700) and 10 deprivation flights (0100, 0500, 0900, 1300, and 1700 on deprivation day 1; and 0100, 0500, 0900, 1300, and 1700 on deprivation day 2) under the influence of placebo versus Dexedrine were analyzed with a 3-way ANOVA for drug, session, and iteration. The iteration factor was added to include each instance of maneuvers that were conducted more than once during the flight profile.

Straight and levels (SLs)

Analysis of the composite scores based on how well subjects controlled heading, altitude, airspeed, and roll during the four iterations of straight-and-level flight (the last of which was flown without the benefit of the AFCS trim system) revealed several interactions and main effects. There was an interaction between drug and session ($F(12,48)=2.34$, $p=.0189$) due to the fact that there were no differences between the two drug conditions at baseline or at 0100 on the first deprivation day, but substantial impairments under placebo relative to Dexedrine occurred at 0500 and 1300 ($p<.05$). Although performance appeared to continue to suffer under placebo at 1700 on this day (see figure 1, first panel), there was no statistically significant difference. However, on the second deprivation day, decrements under placebo were marked at 0100, 0500, 0900, and 1300. Once again, there was a recovery in performance under placebo at the 1700 flight. However, generally speaking, flight control accuracy was preserved from baseline until the end of deprivation by Dexedrine.

There was an interaction between drug and iteration (F(3,12)=13.97, p=.0003) which analysis of simple effects indicated was attributable to poorer performance under placebo versus Dexedrine at SLs 2-4 (p<.05), while a similar effect was absent at SL 1. This can be seen below in figure 1 (second panel).

There were main effects on the drug (F(1,4)=23.61, p=.0083), session (F(12,48)=5.39, p<.0001), and iteration (F(3,12)=21.41, p<.0001) factors. The drug effect was due to the fact that performance was lower overall under placebo in comparison to Dexedrine (the means were 74.0 vs 80.1, respectively). The session effect resulted from the presence of significant linear, quadratic, and cubic trends (p<.05). As can be seen in figure 1 (third panel), averaging placebo and Dexedrine conditions at each flight showed a general decline in control accuracy from baseline to the end of the deprivation period which was particularly noticeable in the circadian trough at 0500 and 0900 on both deprivation days (note that this was primarily due to decrements under placebo). The iteration effect occurred because performance on SL 1 was better than performance on SLs 2-4 (p<.05), performance on SL 2 was better than performance on SL 4 (p<.05), and performance on SL 3 tended to be better than performance on SL 4 (p=.0578). The means for the four straight and levels were 82.5, 77.9, 74.7, and 73.1, respectively.

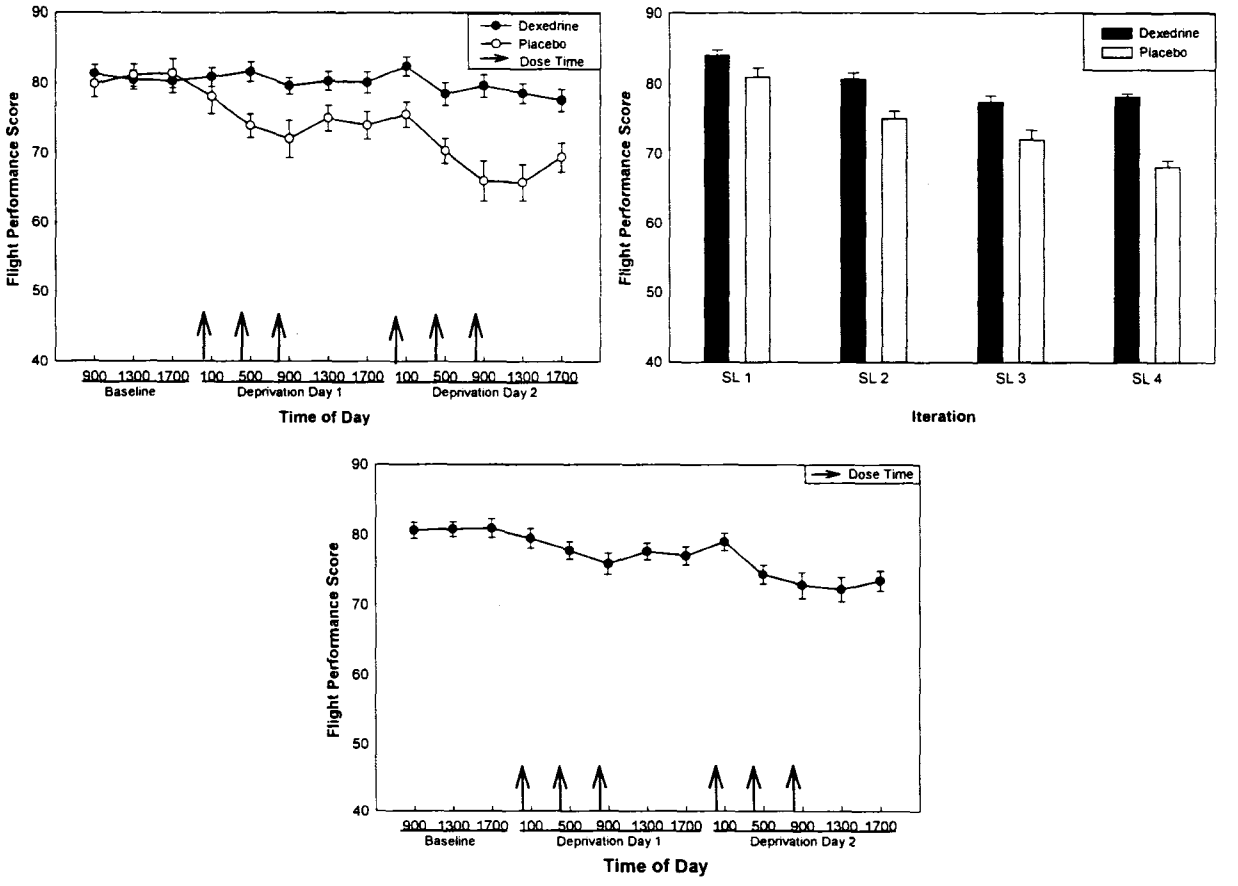

Figure 1. Effects of drug and session (top left), drug and iteration (top right), and session (bottom center) on flight performance in the SLs.

Climbs

Analysis of the composite scores based on heading, airspeed, slip, roll, and vertical speed control during both iterations of this maneuver (one of which was a 500-foot climb and the other of which was a 1000-foot climb) revealed three drug-related effects. There was an interaction between drug and session ($F(12,48)=1.96$, $p=.0501$) due to the absence of condition differences prior to the decrements under placebo at 0900 and 1700 on the first deprivation day. On the second deprivation day, flight scores were marginally lower under placebo than Dexedrine at 0500 ($p=.0569$), but there were no effects at subsequent times (see figure 2).

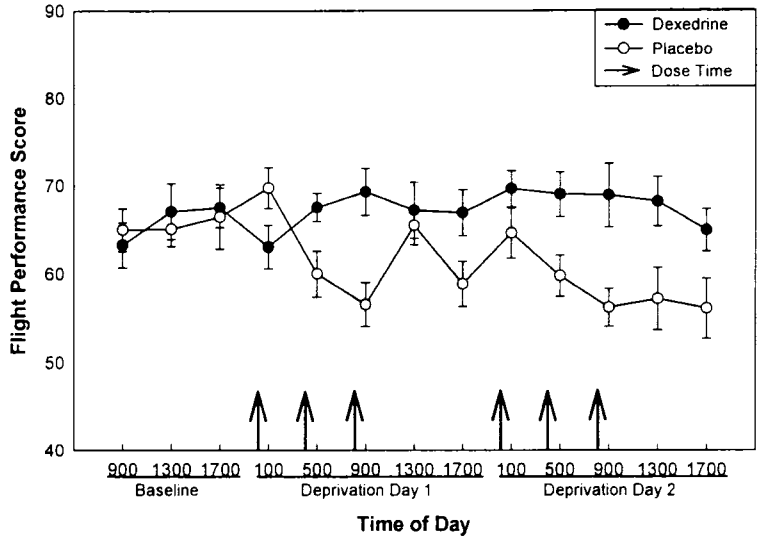

Figure 2. Effects of drug and session on the climb.

An interaction between drug and climb ($F(1,4)=8.36$, $p=.0445$) was attributable to the difference between placebo and Dexedrine during the first ($p<.05$), but not the second climb. Aviators flew less precisely under placebo than Dexedrine only on the first iteration of this maneuver (the means were 61.4 and 70.1, respectively).

There was a main effect on the drug factor ($F(1,4)=19.30$, $p=.0118$) which occurred because of an overall decrement in performance under placebo which was attenuated by Dexedrine. The means of the placebo and Dexedrine conditions were 61.6 vs 67.1, respectively.

Descents

Analysis of the composite of heading, airspeed, slip, roll, and vertical speed scores from the three descents (two of which were 500-foot descents and one of which was a 1000-foot descent, all flown without the aid of the AFCS trim system) revealed one interaction and two main effects. The interaction was between the drug and session factors ($F(12,48)=2.73$, $p=.0067$). Analysis of simple effects indicated first that there were no differences between placebo and Dexedrine at any of the baseline sessions or at 0100 on the first deprivation day. However,

performance under placebo was poorer than performance under Dexedrine at 0500, 0900, 1300, and 1700 on the first deprivation day, and at 0500, 0900, and 1300 on the second deprivation day ($p \leq .05$). Performance tended to be poorer ($p=.0563$) at 1700 on this day as well (see figure 3).

There were main effects on the drug and session factors. The drug effect ($F(1,4)=30.17$, $p=.0054$) was due to an overall drop in performance under placebo that was prevented by administration of Dexedrine (the means were 48.8 and 56.2, respectively). The session effect ($F12,48)=3.14$, $p=.0023$) was attributable to the presence of linear, quadratic, and cubic trends in the data ($p<.05$). The averaged placebo/Dexedrine scores from each of the flights revealed a general decline in performance from baseline until the end of the deprivation period (see figure 3). The decrements were more pronounced at some times than at others due to circadian effects. Note that most of the changes in flight scores were the result of averaging in the placebo condition, since performance under Dexedrine did not drop substantially (relative to baseline).

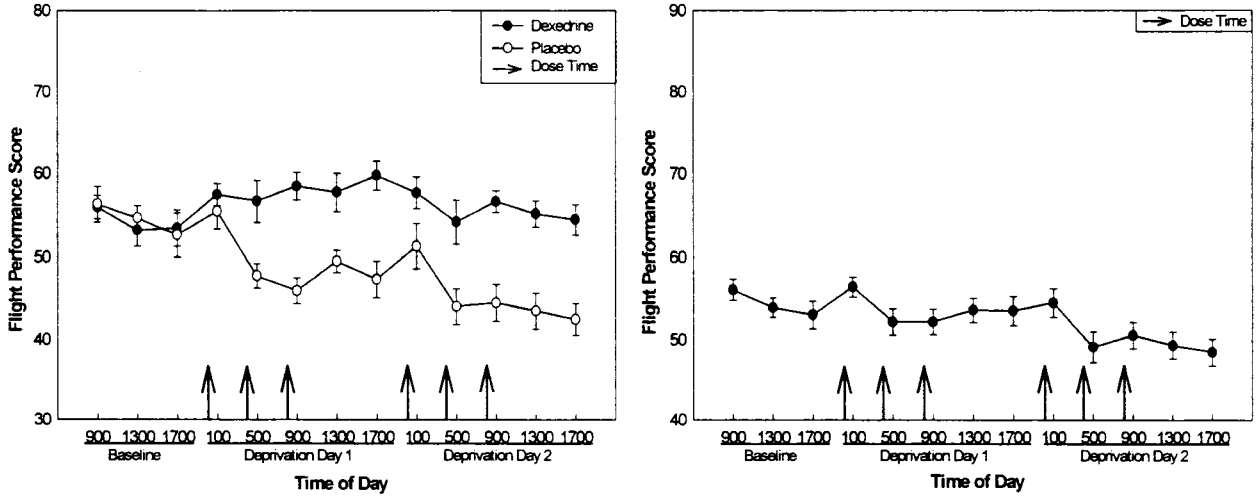

Figure 3. Effects of the combination of drug and session (left panel) and the effects of session, with the other factors collapsed, (right panel) on performance of the descents.

Left standard-rate turns (LSRTs)

Analysis of the composite scores based upon how well subjects maintained turn rate, airspeed, slip, roll, and vertical speed during the two LSRTs (one of which was a 360-degree turn with the AFCS trim system on and one of which was a 180-degree turn with the trim system off) showed several effects. There was a drug-by-session interaction ($F(12,48)=2.07$, $p=.0378$) which was examined with analysis of simple effects. This indicated there were no drug versus placebo differences during any of the baseline sessions or the 0100, 0500, and 0900 sessions on the first deprivation day, but there were differences later (see figure 4). Specifically, flight control was less accurate under placebo than Dexedrine at 1300 (but not 1700) on the first deprivation day and at 0900, 1300, and 1700 on the second deprivation day ($p<.05$).

There was a marginally significant drug main effect ($p=.0640$) due to a tendency toward poorer overall performance under placebo than under Dexedrine (the means were 61.8 versus

68.1). There was a significant main effect on the session factor as well (F(12,48)=2.59, p=.0097). This was due to the presence of a quadratic and cubic trend in the averaged placebo/Dexedrine scores at each test time. As can be seen in figure 4, flight-control accuracy generally declined from baseline to the end of deprivation and was impaired more at some times of the day than at others, probably because of the impact of circadian rhythms. Most of these changes, however, were attributable to the placebo rather than the Dexedrine condition. There was a main effect on the iteration factor (F(1,4)=193.78, p=.0002) attributable to better performance on the first turn than the second (the means were 73.1 and 56.9, respectively).

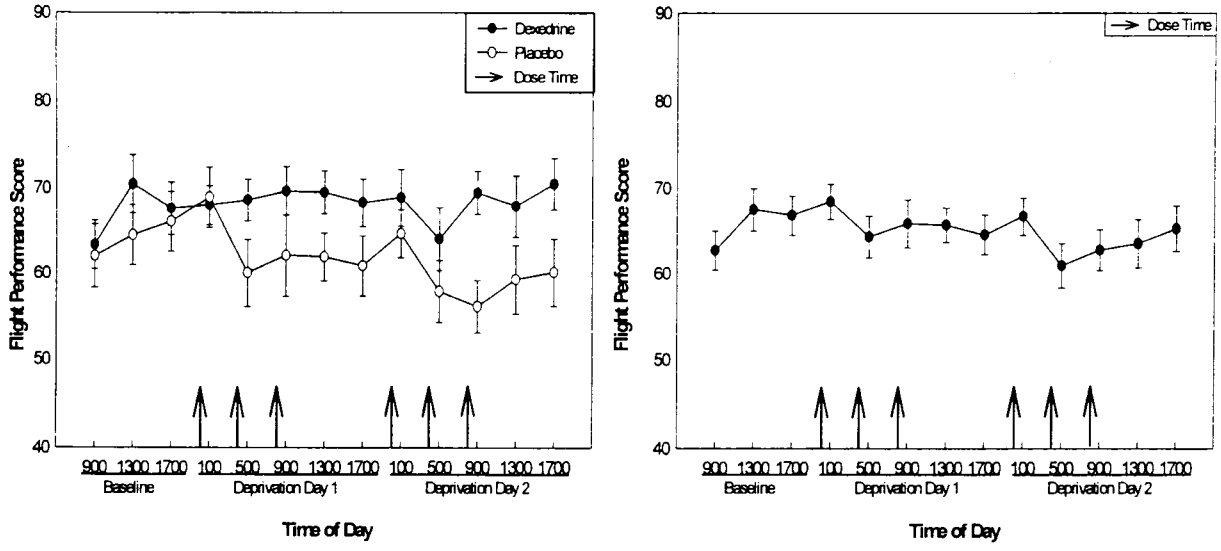

Figure 4. Effects of the drug and session combined (left panel) and session, with the otherfactors collapsed, (right panel) on the left standard-rate turns.

Right standard-rate turns (RSRTs)

The composite scores for the RSRTs (two of which were 180-degree turns flown with the AFCS trim system off and one of which was a 360-degree turn flown with the trim system engaged) were based on the average of turn rate, altitude, airspeed, slip, and roll scores. There was a drug-by-session effect (F(12,48)=2.57, p=.0103) which was due to the absence of a difference between the placebo and Dexedrine conditions at baseline and at 0100 on the first deprivation day followed by several drug-related differences afterward. Specifically, performance under placebo was lower relative to Dexedrine at 0500 and 1700 on the first deprivation day and at 0100, 0900, and 1300 on the second deprivation day (see figure 5).

There were main effects on the drug (F(1,4)=21.25, p=.0100), session (F(12,48)=3.17, p=.0022), and iteration (F(2,8)=15.72, p=.0103) factors. The drug effect was because of a decrement in performance under placebo that was attenuated by Dexedrine (the means were 63.4 and 68.2, respectively). The session effect was due to significant linear, quadratic, and cubic trends (p<.05). The averaged placebo and Dexedrine scores at each of the flights produced a performance curve which steadily declined from baseline to the end of the deprivation period

(see figure 5). This was more pronounced at some times of day than at others due to circadian factors. The reductions in averaged performance at these times (following baseline) were largely attributable to problems within the placebo condition, although peformance under Dexedrine declined as well toward the end of the testing period. The iteration effect was attributable to better performance during the RSRTs which were short and flown with the benefit of the AFCS trim system than the one RSRT that was longer (a 2-minute, 360-degree turn) and flown without the trim system engaged. The means for each iteration were 67.0, 68.5, and 61.8, respectively.

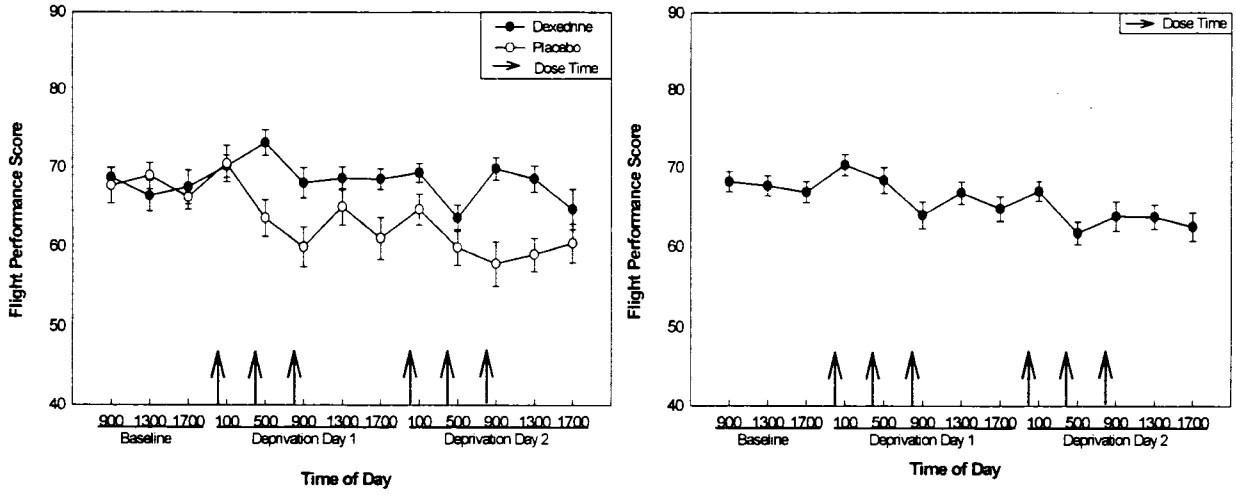

Figure 5. Effects of drug and session combined (left panel) and session, with the other factors collapsed, (right panel) on the right standard-rate turns.

Left descending turn (LDT).

The composite score on the LDT was an average of scores for turn rate, airspeed, slip, roll, and vertical speed. The ANOVA revealed an interaction between drug and session ($F_{912,48}=3.38$, $p=.0013$) which was due to the fact that there were no differences between placebo and Dexedrine at the 0900 and 1300 flights on the baseline day, but performance was poorer at the end of the placebo baseline than at the end of the Dexedrine baseline ($p<.05$). Flight control was clearly affected by drug condition during several of the deprivation-day flights (see figure 6). Although flight accuracy (placebo versus Dexedrine) was not different at 0100 on the first deprivation day, the scores under placebo were lower than those under Dexedrine at 0500 ($p<.05$), marginally lower at 0900 ($p=.0653$), and substantially lower at 1300 ($p<.05$). These placebo-related decrements were not present at 1700 or in the next flight which occurred at 0100. However, at 0500 and 0900 on the second deprivation day, flight control again declined under placebo whereas Dexedrine attenuated this effect. There were no significant differences between the two drug conditions at 1300 or 1700.

EEG

The absolute power data from the resting eyes-open/eyes-closed EEG was analyzed in four parts using a series of 3-way ANOVAs (one each for delta, theta, alpha, and beta activity).

Although the initial data set consisted of EEG recordings from Fz, C3, Cz, C4, Pz, O1, and O2, only a subset of these electrodes were analyzed because of the presence of recording aritifacts (primarily from muscle-activity contamination). Visual inspection of data from all sites indicated that EEG activity from Fz, Cz, and Pz was of sufficient quality to warrant further analysis (at the most, about 17 percent of the data was contaminated at some of the testing times, and these instances were set to missing in the data file and then estimated using the mean of the "clean" data before the ANOVAs were performed). The ANOVAs consisted of three factors: condition (placebo versus Dexedrine), session (1015, 1415, and 1815 on baseline; 0215, 0615, 1015, 1415, and 1815 on deprivation day 1; and 0215, 0615, 1015, 1415, and 1815 on deprivation day 2), and eyes (eyes open/eyes closed).

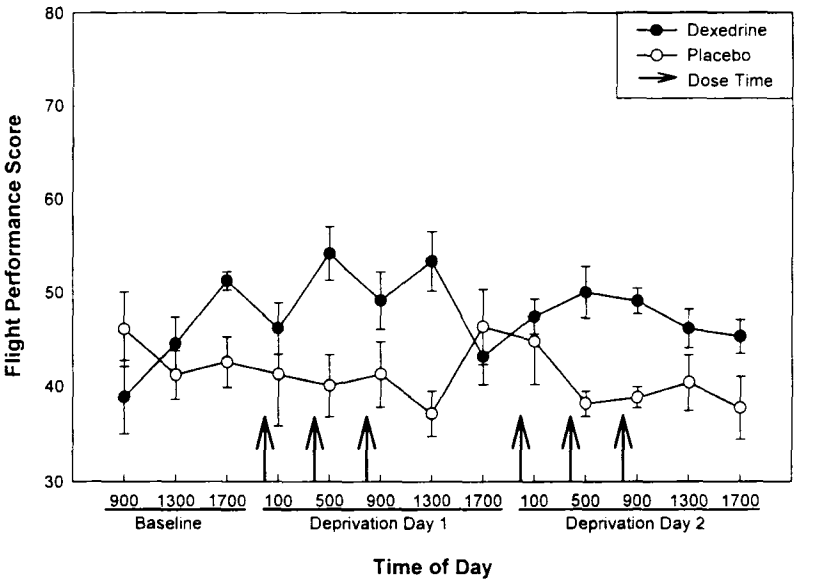

Figure 6. Effects of drug and session on the left descending turn.

Delta activity

Analysis of delta activity (1.5-3.0 Hz), the slowest-wave EEG indicative of fatigue or sedation in awake subjects, revealed several effects. A session-by-eyes interaction at Fz ($F(12,48)=2.04$, $p=.0403$) was due to significant differences in the delta activity recorded under eyes open versus eyes closed at every testing time except 0215 and 1015 on the first deprivation day and 1415 on the second deprivation day. However, as can be seen below, the pattern of effects (increased delta as a function sleep deprivation) was quite similar regardless of whether eyes were open or closed. There was a drug-by-eyes interaction as well at Fz ($F(1,4)=7.99$, $p=.0475$). This was due to the fact that, although there was more delta activity under placebo than Dexedrine both with eyes open and with eyes closed, the difference was larger with eyes closed ($p<.05$). Both the session-by-eyes and drug-by-eyes interactions are depicted in figure 7.

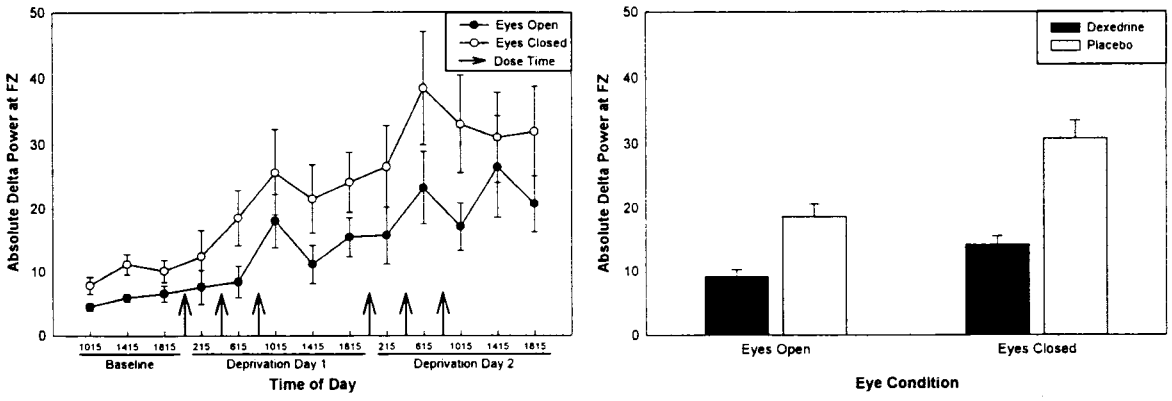

Figure 7. Effects of eye closure and session (left panel) and the effects of eye closure and drug (right panel) on EEG delta activity.

There were drug-by-session effects at Fz ($F(12,48)=2.50$, $p=.0124$), Cz ($F(12,48)=2.15$, $p=.0303$), and Pz ($F(12,48)=2.10$, $p=.0352$). Analysis of simple effects showed that at every recording site, there was more delta under placebo than Dexedrine at 0615 and 1415 on the first deprivation day and at 0215, 1015, and 1415 on the second deprivation day ($p<.05$ except for Fz delta at 1415 and Pz delta at 1015 where the p values were .0665 and .0618, respectively). These interactions are depicted in figure 8.

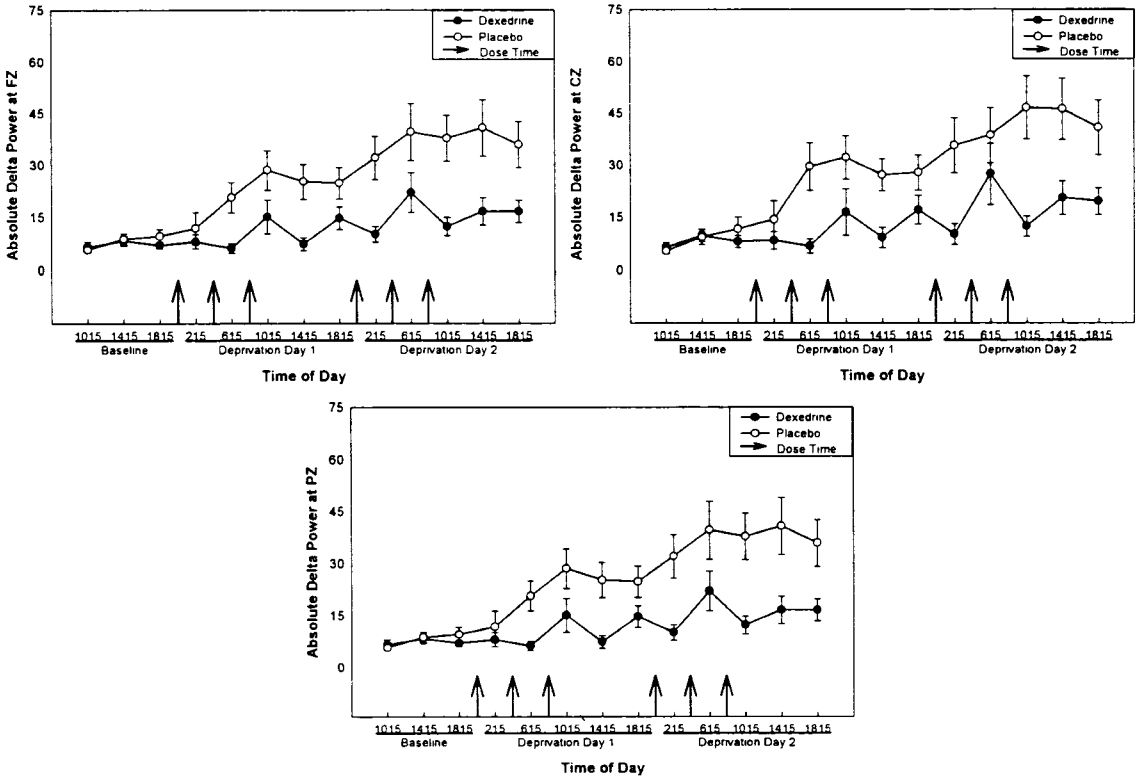

Figure 8. The effects of drug and session EEG delta activity at Fz (top left), Cz (top right), and Pz (bottom center).

There were main effects on the drug factor at Fz ($F(1,4)=11.58$, $p=.0272$), Cz ($F(1,4)=12.67$, $p=.0236$), and Pz ($F(1,4)=11.12$, $p=.0290$) attributable to higher delta power under placebo than Dexedrine. There were main effects on the session factor at Fz ($F(12,48)=6.97$, $p<.0001$), Cz ($F(12,48)=7.45$, $p<.0001$), and Pz ($F(12,48)=6.59$, $p<.0001$) due to the presence of significant linear, quadratic, and cubic trends ($p<.05$) at all three sites. As can be seen in figure 9, there was a deprivation-related increase in delta activity which was particularly pronounced at 1015 on the first deprivation day and 0615 on the second day, probably due to the influence of circadian rhythms. There was a main effect on the eyes factor at Fz ($1,4)=16.75$, $p=.0149$), Cz ($F(1,4)=14.69$, $p=.0186$), and Pz ($F(1,4)=9.71$, $p=.0356$), all of which occurred because delta activity was higher under eyes closed than eyes open.

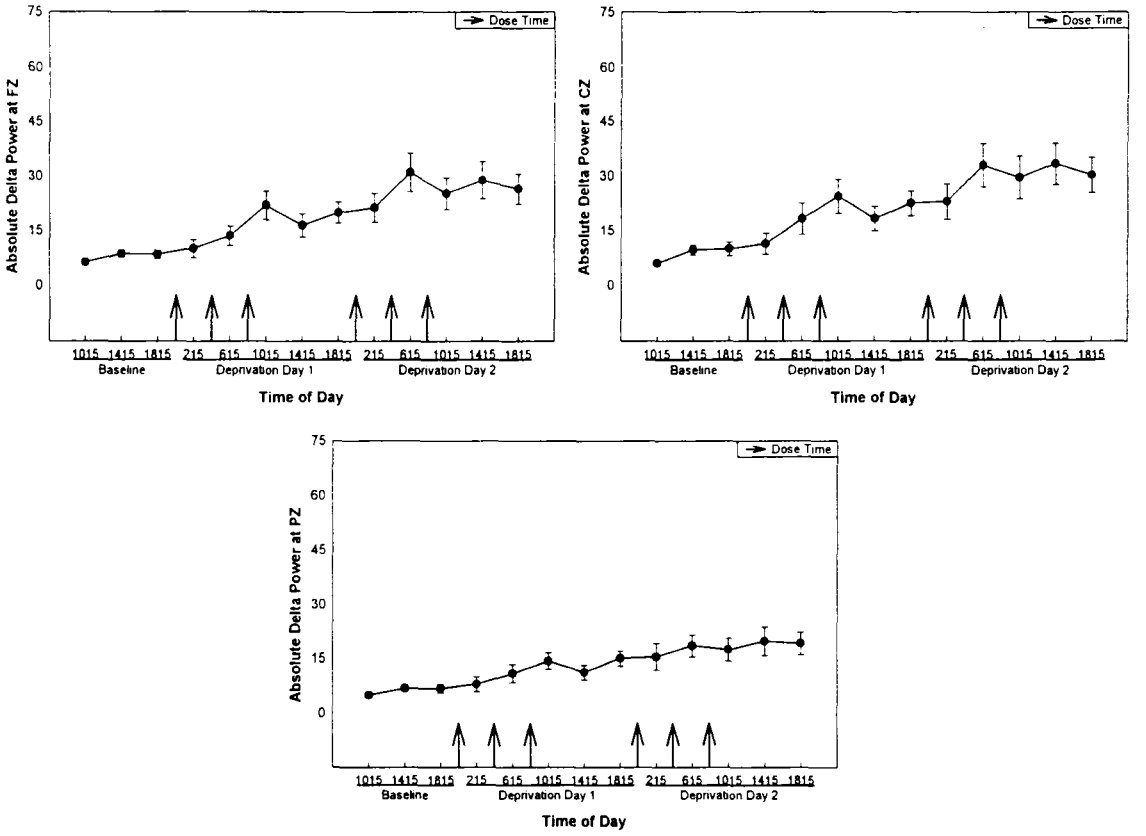

Figure 9. Effects of session with all other factors collapsed on EEG delta activity at Fz (top left), Cz (top right), and Pz (bottom center).

Theta activity

Analysis of theta activity (3.0-8.0 Hz), which is faster than delta but still considered to be slow-wave EEG known to increase with sleep deprivation, showed there was a 3-way interaction among drug, session, and eyes at Cz ($F(12,48)=2.31$, $p=.0202$) and Pz ($F(12,48)=2.54$, $p=.0110$). Analysis of simple effects revealed drug-by-session interactions both under eyes open and under eyes closed at Cz ($p\leq.05$), but at Pz, there was a drug-by-session interaction only under eyes open ($p<.05$). Although the interactions at Cz (within each of the eyes conditions) appeared

similar, subsequent analyses of simple effects showed there were minor differences. Under eyes open at Cz, there was more theta under placebo than Dexedrine at 0615, 1015, and 1415 on the first deprivation day and more theta under placebo than Dexedrine at 0215 and 1415 on the second deprivation day ($p \leq .05$). Under eyes closed at Cz, the effects were similar, but often not as robust. There was more theta under placebo than Dexedrine at 0615, 1015 ($p=.0551$), and 1415 on the first deprivation day and at 0215, 1015 ($p=.0559$), and 1815 on the second deprivation day. Note that the difference at 1415 that appeared under eyes open was not significant with eyes closed. The interaction at Pz was more straightforward in that there was no drug-by-session effect at eyes closed, whereas there was one at eyes open. Under eyes open, there was more theta under placebo than Dexedrine at 0615, 1015, and 1415 on the first deprivation day and at 0215, 1415, and 1815 on the second deprivation day. The interactions between drug and session as a function of eye closure are depicted in figure 10.

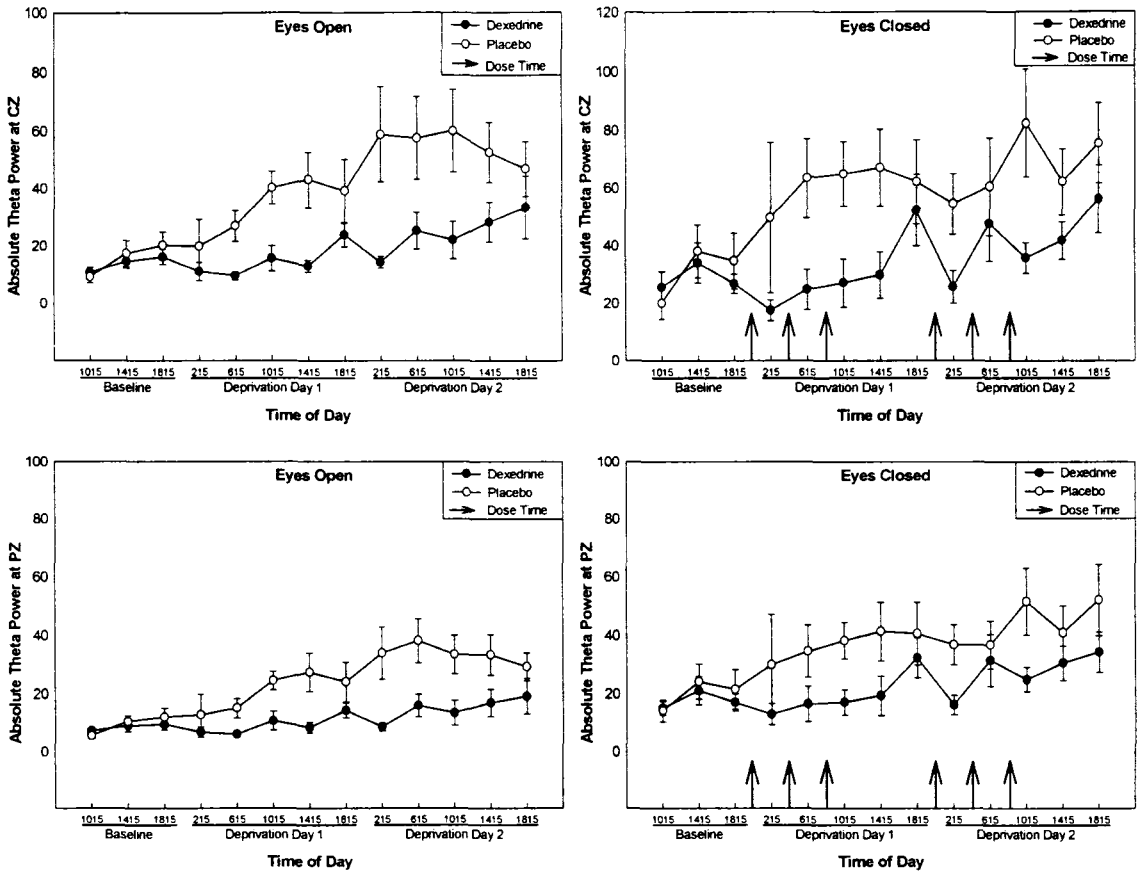

Figure 10. The effects of drug, eye closure, and session on EEG theta activity at Cz (top) and Pz (bottom).

There was a session-by-eyes interaction at Cz ($F(12,48)=1.92$, $p=.0549$) because there was more theta under eyes closed than eyes open at every testing session, with the exception of 0215 on the first deprivation day and 0215 and 1415 on the second deprivation day (see figure 11).

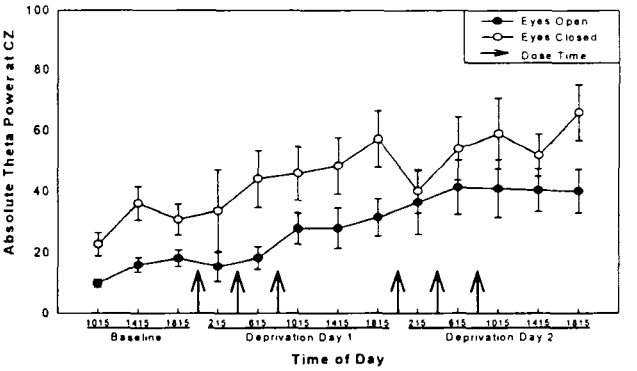

Figure 11. Effects of eye closure and session on EEG theta activity at Cz.

There were drug-by session interactions at Fz ($F(12,48)=2.85$, $p=.0050$), Cz ($F(12,48)=2.35$, $p=.0183$), and Pz ($F(12,48)=2.05$, $p=.0396$). At each site, there were no differences between placebo and Dexedrine during baseline (predrug), but there was more theta under placebo than Dexedrine at 0615 and 1015 on the first deprivation day and at 0215, 1415, and 1815 on the second deprivation day ($p<.05$). In addition, there was a difference on the first deprivation day between the drug conditions at 1415 for Cz ($p<.05$), a marginally-significant difference at 1415 for Pz ($p=.0617$), and no difference at 1415 for Fz. On the second deprivation day, there was a significant difference at 1015 for Fz ($p<.05$), a marginally-significant difference for Cz ($p=.0608$), and no difference for Pz. These drug-by-session interactions are shown in figure 12.

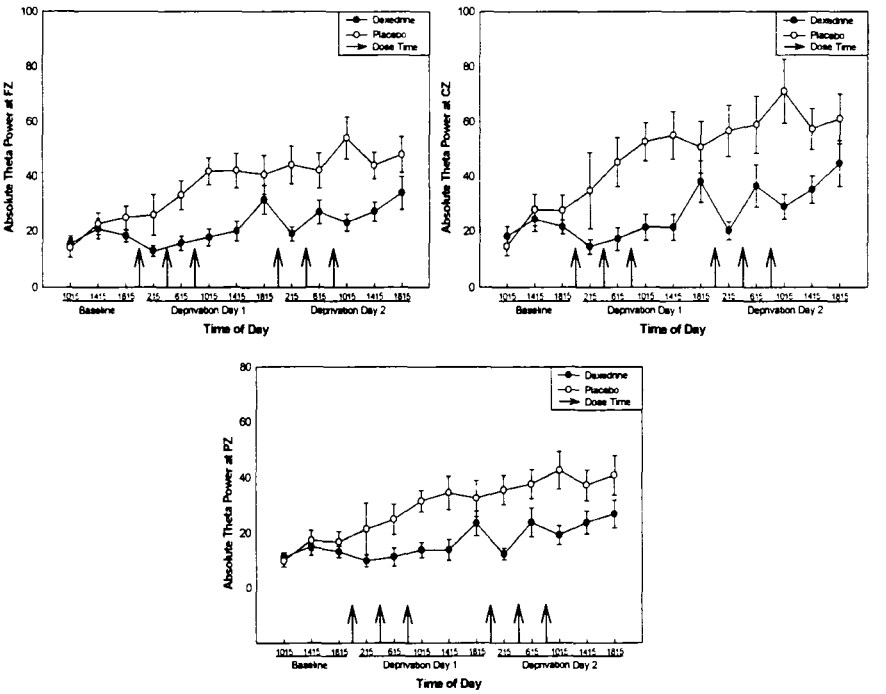

Figure 12. Effects of drug and session on EEG theta at Fz (top left), Cz (top right), and Pz (bottom center).

There were main effects on the drug factor at Fz ($F(1,4)=9.74$, $p=.0355$), Cz ($F(1,4)=8.73$, $p=.0418$), and Pz ($F(1,4)=10.14$, $p=.0334$) due to more theta under placebo than Dexedrine. There were main effects on the session factor at Fz ($F(12,48)=5.95$, $p<.0001$), Cz ($F(12,48)=5.60$, $p<.0001$), and Pz ($F(12,48)=5.98$, $p<.0001$) attributable to significant linear, quadratic, and cubic trends at each ($p<.05$). As can be seen in figure 13, there was a gradual deprivation-related increase in theta activity that was more pronounced at some times than at others due to the influence of circadian factors. There were main effects on the eyes factor at Fz ($F(1,4)=24.91$, $p=.0075$), Cz ($F(1,4)=17.76$, $p=.0135$), and Pz ($F(1,4)=14.51$, $p=.0190$) all of which were due to increased theta under eyes closed versus eyes open.

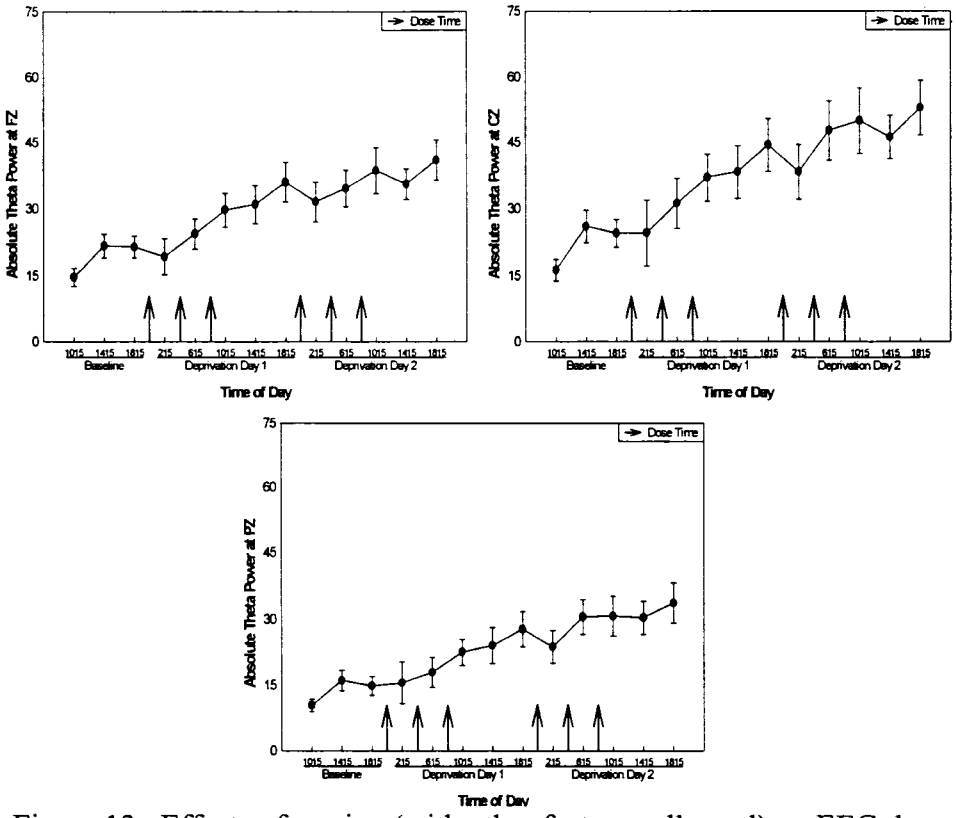

Figure 13. Effects of session (with other factors collapsed) on EEG theta activity at Fz (top left), Cz (top right), and Pz (bottom center).

Alpha activity

Analysis of alpha activity (8.0-13.0 Hz), which is predominant during relaxed wakefulness under eyes closed, but is suppressed during sleep, indicated there was a drug-by-time-by-eyes interaction at Fz ($F(12,48)=3.56$, $p=.0008$) and Cz ($F(12,48)=2.16$, $p=.0300$). Analysis of simple effects revealed these 3-way interactions were attributable to the fact that there was no drug-by-session interaction under eyes open at either Fz or Cz; however, there were drug-by-session interactions under eyes closed ($p<.05$). Further analyses showed there were no drug-related differences at any of the baseline sessions (predrug) for either Fz or Cz, but there was

substantially less eyes-closed alpha under placebo than Dexedrine at 0615 on the first deprivation day ($p<.05$) and at 0215 on the second deprivation day (however, this latter effect for Fz was only marginally significant, $p=.0597$). In the last session of the second deprivation day, there was a rebound effect at Fz where there was more eyes-closed alpha under placebo than Dexedrine (see figure 14).

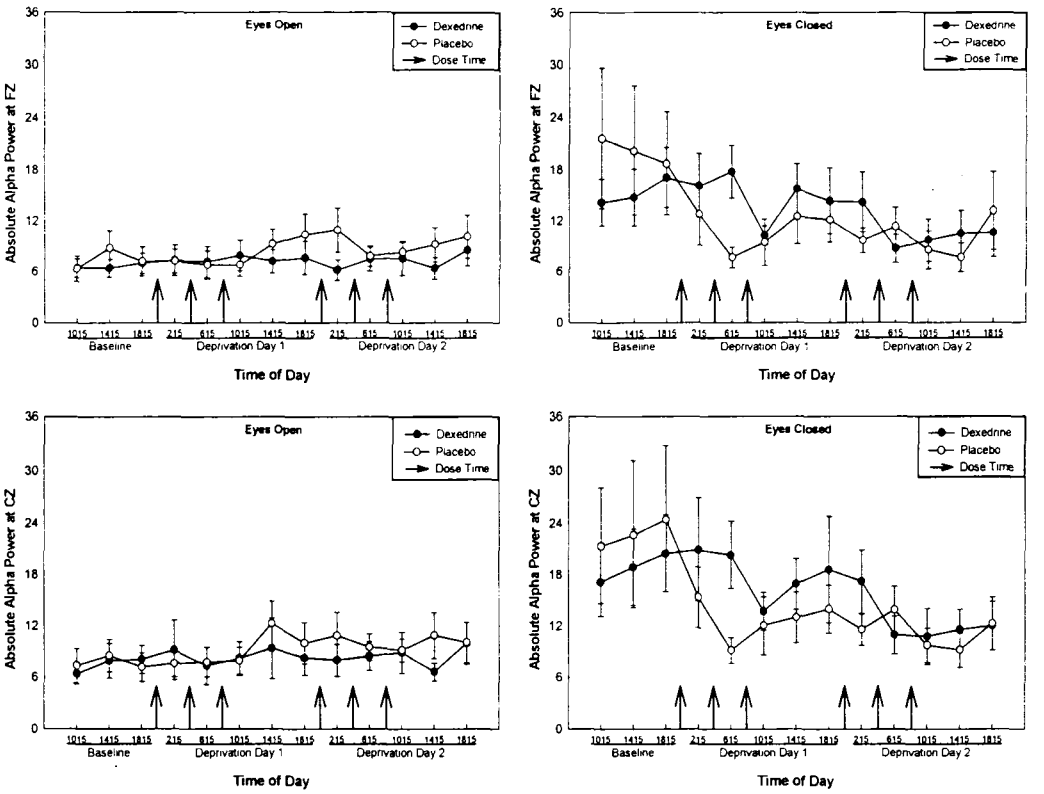

Figure 14. Effects of drug, eye closure, and session on EEG alpha activity at Fz (top) and Cz (bottom).

There was a session-by-eyes interaction at Fz ($F(12,48)=6.36$, $p<.0001$), Cz ($F(12,48)=8.45$, $p<.0001$), and Pz ($F(12,48)=16.07$, $p<.0001$). Analysis of simple effects showed that, in most cases, alpha activity was much higher with eyes closed than eyes open during baseline, but the difference became smaller as deprivation progressed. There were significant differences between eyes open and eyes closed at all three electrodes at 1015, 1415, and 1815 during baseline, and at 0215, 0615, and 1815 during the first deprivation day (also, there was a similar effect at Fz and Pz at 1415). By the second deprivation day, there were no differences at any of the sessions at Fz, only one at Cz (at 0215), and only two at Pz (0215 and 0615). These session-by-eyes effects are shown in figure 15.

There was a drug-by-session interaction at Fz ($F(1,4)=1.98$, $p=.0476$) due to the fact that alpha was higher under placebo than Dexedrine at 1415 on the baseline day (predrug), but lower under placebo than Dexedrine at 0615 on the first deprivation day ($p<.05$). There were no drug-related differences elsewhere (see figure 16).

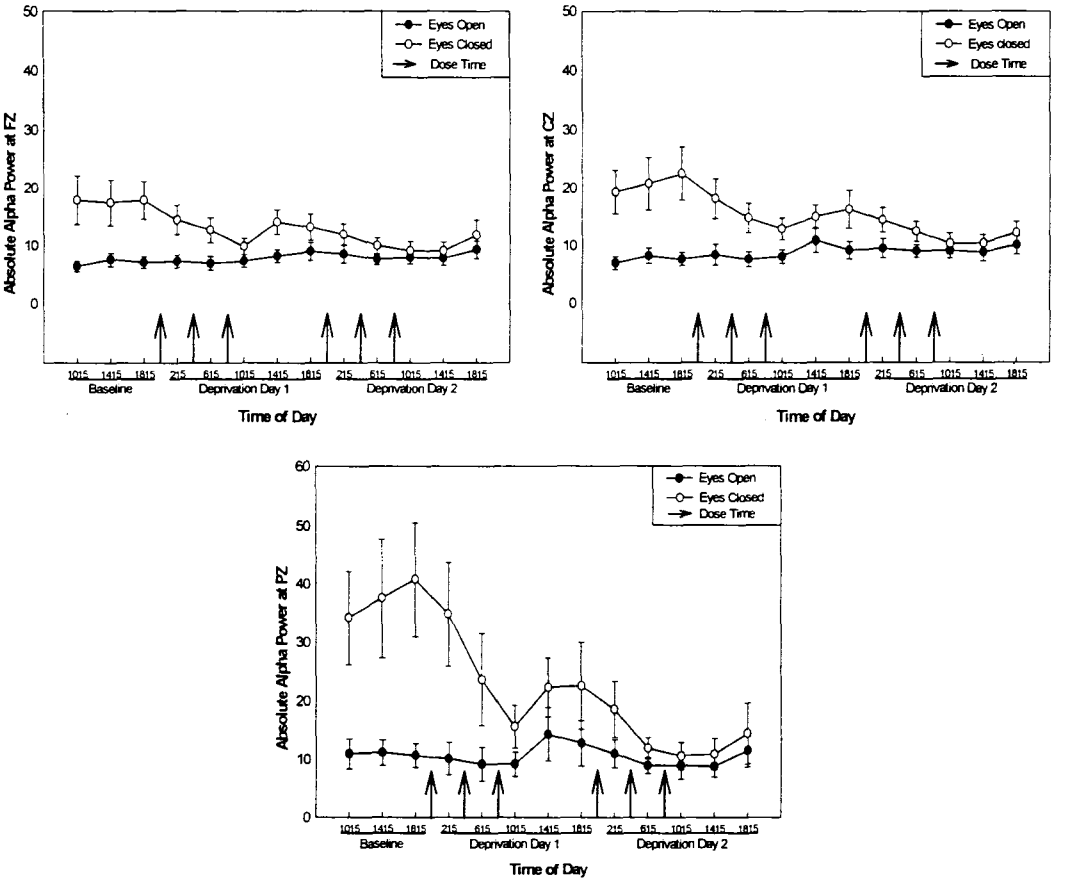

Figure 15. Effects of eye closure and session on EEG alpha activity at Fz (top left), Cz (top right), and Pz (bottom center).

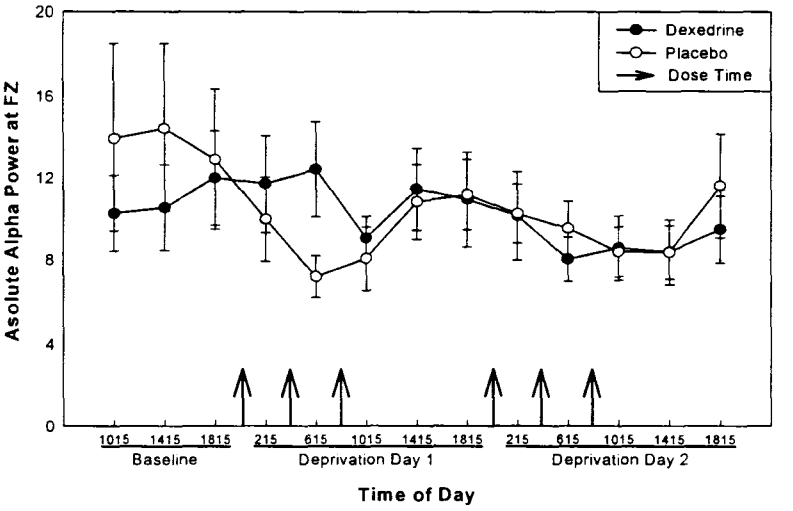

Figure 16. Effects of drug and session on alpha activity at Fz.

There were no main effects on the drug factor for alpha activity. However, there were session main effects at Fz ($F(12,48)=3.12$, $p=.0025$), Cz ($F(12,48)=5.15$, $p<.0001$), and Pz ($F(12,48)=9.76$, $p<.0001$). Trend analysis showed there were significant linear, quadratic, and cubic trends at all three recording sites. As can be seen in figure 17, there was a gradual decline in alpha activity as deprivation progressed, but there were recovery peaks at about 1815 on both days with troughs at about 1015 (probably because of circadian rhythms). There were main effects on the eyes factor at Fz ($F(1,4)=30.21$, $p=.0053$), Cz ($F(1,4)=133.78$, $p=.0003$), and Pz ($F(1,4)=53.47$, $p=.0019$), all of which were due to greater alpha activity under eyes closed than under eyes open.

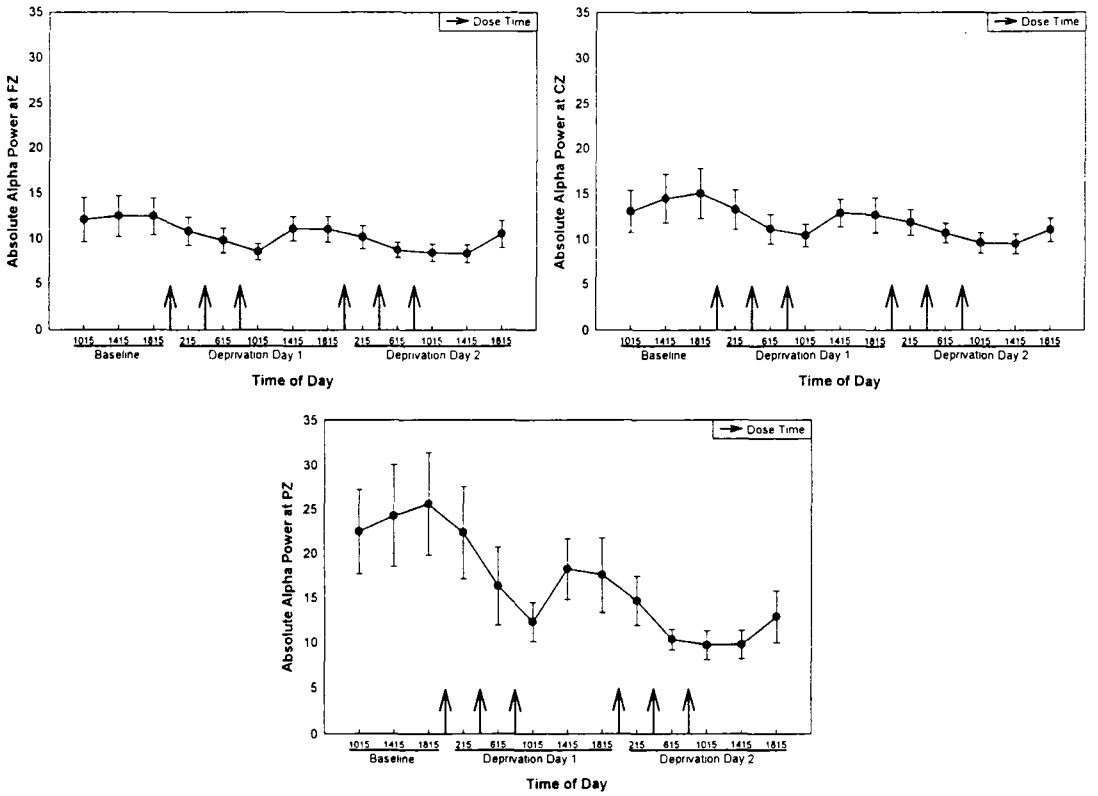

Figure 17. Effects of session (with all other factors collapsed) on EEG alpha at Fz (top left), Cz (top right), and Pz (bottom center).

Beta activity

Analysis of beta activity (13.0-20.0 Hz), which is the fastest type of EEG activity typically analyzed (it occurs during increased mental concentration and sometimes appears to be increased when contaminated by muscle tension), revealed a significant drug-by-session interaction at Pz ($F(12,48)=2.33$, $p=.0191$) which was because of less beta under placebo than Dexedrine at 1815 on the first deprivation day and more beta under placebo than Dexedrine at the same time on the second deprivation day ($p<.05$). There were no differences between the drug conditions at any of the other times (see figure 18).

There were no drug or eyes main effects on beta activity; however, there was a significant session effect at Fz ($F(12,48)=2.22$, $p=.0256$) which occurred because of marked quadratic and cubic trends in the data ($p<.05$). As can be seen in figure 18, beta activity decreased from base line to 1015 on the first deprivation day, then recovered slightly before decreasing again on the second deprivation day.

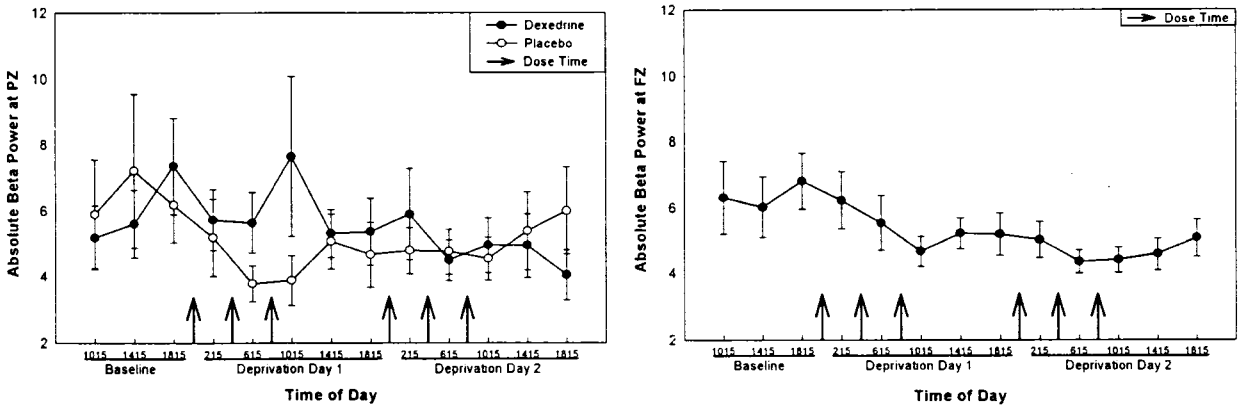

Figure 18. Effects of drug and session on beta activity at Pz (left), and the effects of session with the other factors collapsed on beta activity at Fz (right).

Desktop flight simulator

The desktop flight simulator task consisted of two components. The first was the "flight" portion that yielded a score based on the accuracy and speed with which subjects flew the course. The second was the secondary task that yielded the percentage of target tones to which the subject failed to respond (percent misses) and the reaction time (RT) to the target tones hit. Both components were analyzed using 2-way ANOVA for drug (placebo versus Dexedrine) and session (13 levels: 1045, 1445, and 1845 on the baseline day; 0245, 0645, 1045, 1445, and 1845 on the first deprivation day; and 0245, 0645, 1045, 1445, and 1845 on the second deprivation day).

Scores

The ANOVA on the "flight" scores indicated there were no significant interactions or main effects. An examination of the means showed that performance under placebo evidenced a slight tendency to be lower than performance under Dexedrine, but the variability was far too large for this difference to attain significance.

Tones

The ANOVA on the percent target tones that were missed revealed a drug-by-session interaction ($F(12,48)=3.34$, $p=.0014$). Analysis of simple effects showed this was due to the fact that there were no differences between the two conditions at baseline (predrug), but there was an increase in the number of tones missed under placebo versus Dexedrine at 0645 on the first

deprivation day and at 0645, 1045, and 1845 ($p \leq .05$) on the second deprivation day (see figure 19).

There was an overall drug effect ($F(1,4)=20.65$, $p=.0105$) because of an increase in the number of tones missed under placebo versus Dexedrine (25.6 percent versus 18.0 percent). In addition, there was a session main effect ($F(12,48)=4.10$, $p=.0002$) attributable to significant quadratic and cubic trends in the data ($p<.05$). As can be seen in figure 19, averaged performance revealed a circadian effect which resulted in impaired performance at 0245 on the first and second deprivation days (relative to the other times). Note that this effect was due largely to the influence of the placebo condition whereas Dexedrine attenuated these problems.

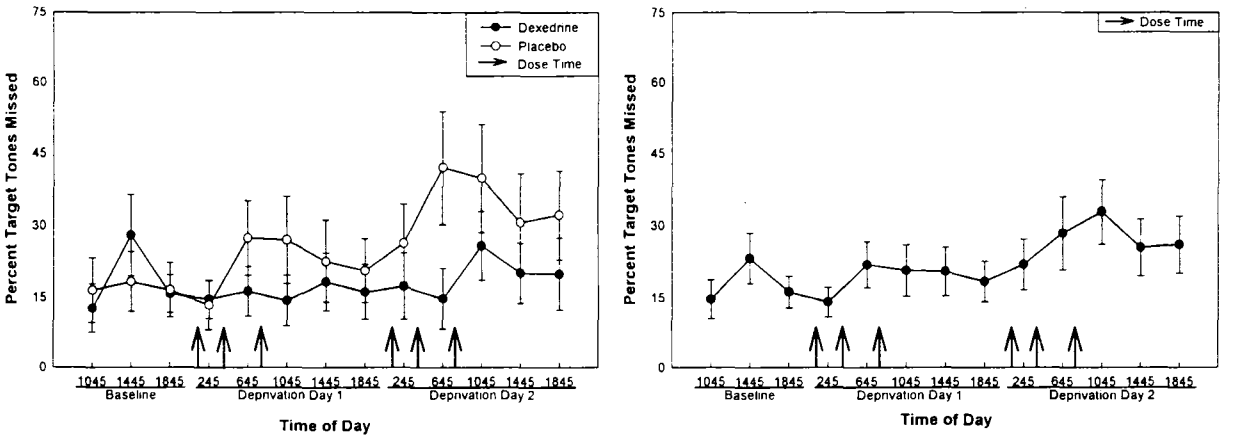

Figure 19. Effects of drug and session and session (with the other factors collapsed) on the number of targets missed during the desktop flight simulation task.

The ANOVA on the RT to target tones indicated a drug-by-session interaction ($F(12,48)=3.40$, $p=.0012$). Analysis of simple effects (comparing placebo and Dexedrine at each testing time) showed there were no differences at any of the baseline sessions, or any of the sessions on the first deprivation day, but RT was substantially slower under placebo than Dexedrine ($p<.05$) at 0645 and 1045 on the second deprivation day (see figure 20). There was no overall drug effect on this variable, but there was a session main effect ($F(12,48)=2.51$, $p=.0120$) which was due to the presence of significant quadratic and cubic trends in the data. As can be seen in figure 20, RTs decreased at about 1045, probably as a function of circadian-related changes in alertness on both deprivation days. RTs in between these two times were similar to those on the baseline day (before the subjects were well-trained on the task). This effect should be interpreted cautiously since there was a higher-order interaction on RTs (behavior under Dexedrine was different than behavior under placebo).

POMS

The factor scores collected during 4 baseline sessions (1120, 1520, 1920, and 2340) and 12 deprivation sessions (0320, 0720, 1120, 1520, 1920, and 2340 on deprivation day 1; and at 0320, 0720, 1120, 1520, 1920, and 2225 on deprivation day 2) under the influence of placebo versus Dexedrine were analyzed in a series of 2-way ANOVAs for drug and session. The 2340 scores

and the 2225 scores for each scale were placed in the same level of the session factor for ease of analysis (the earlier test time at the end of deprivation day 2 was necessary to ensure that subjects could initiate recovery sleep by 2300). Each of the factors (tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment) was analyzed separately.

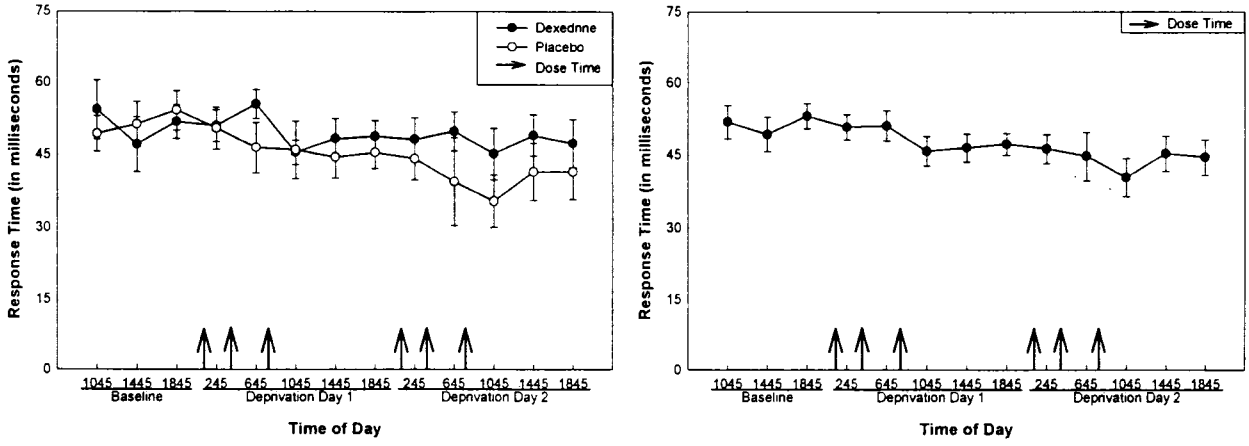

Figure 20. Effects of drug and session (left) and session with the other factors collapsed (right) on reaction times to target tones during the desktop simulation task.

Tension-anxiety scale

The 2-way ANOVA on the tension-anxiety scale, which reflects heightened musculoskeletal tension, indicated there was no drug-by-session interaction and no drug main effect. There was, however, a significant session main effect ($F(15,60)=2.60$, $p=.0046$) which was due to the presence of quadratic and cubic trends in the data from this scale ($p \leq .05$). As can be seen in figure 21, tension-anxiety scores were relatively low during the beginning, middle, and end of each subject's participation. However, at 0720 on both deprivation days, there were increases which were probably due to circadian effects.

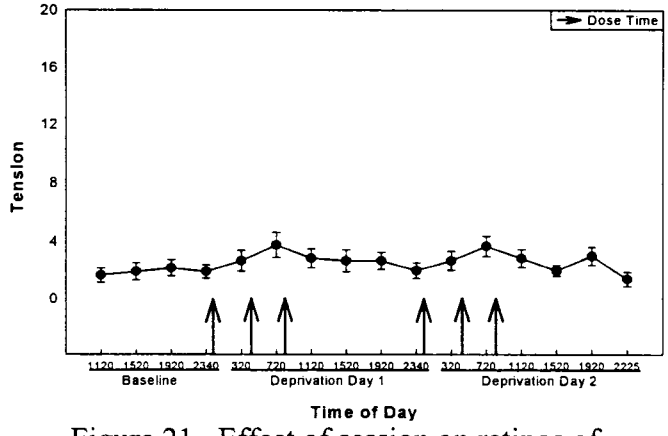

Figure 21. Effect of session on ratings of POMS tension-anxiety.

Depression-dejection scale

The scores on the depression-dejection scale, which measures despondence and sadness, also indicated no drug-by-session interaction or drug main effect. However, as was the case with tension-anxiety scores, there was a significant session main effect ($F(15,60)=1.83$, $p=.0506$). Trend analysis indicated this was due to a significant cubic trend which resulted from the circadian-related peaks in scores at 0720 on both deprivation days (see figure 22).

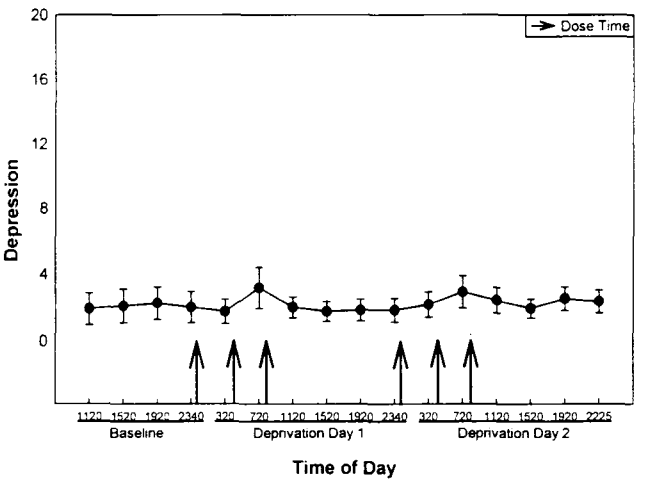

Figure 22. Effect of session on POMS ratings of depression-dejection.

Anger-hostility scale

The 2-way analysis of variance on anger-hostility scores, which reflect anger and antipathy towards others, indicated no significant interaction or session main effect; however, there was a drug main effect ($F(1,4)=9.76$, $p=.0354$). This was attributable to a slight deprivation-related increase under placebo which was attenuated by Dexedrine (the means were 0.4 and 0.6, respectively).

Vigor-activity scale

The ANOVA on vigor-activity scores, which reflect energy levels, revealed several effects. There was a drug-by-session interaction ($F(15,60)=4.69$, $p<.0001$) which analysis of simple effects indicated was due to the fact that there were no condition differences during any of the baseline sessions, but substantially lower vigor scores under placebo than under Dexedrine at 0320, 0720, 1120, 1520, and 2340 on the first deprivation day and at 0320 on the second deprivation day ($p<.05$). There were no differences between the two drug conditions after 0320, toward the end of the 64-hour deprivation period (see figure 23). In addition, there were main effects on both the drug ($F(1,4)=8.19$, $p=.0458$) and session $F(15,60)=10.78$, $p<.0001$) factors.

The drug effect was because vigor ratings were lower overall under placebo in comparison to Dexedrine (the means were 13.9 and 19.6, respectively). The session effect was due to the presence of significant linear, quadratic, and cubic trends ($p<.05$). As can be seen in figure 23, vigor-activity scores generally declined from the begining to the end of deprivation, although there were intermittent plateaus due to the fact that while Dexedrine was improving vigor ratings, substantial reductions were occurring under placebo. Also, note that there was an overall drop in vigor ratings at 0720 on the second deprivation day which was followed by an increase at the end of the deprivation period. Caution is advised in interpreting these session effects since there was a significant higher-order interaction.

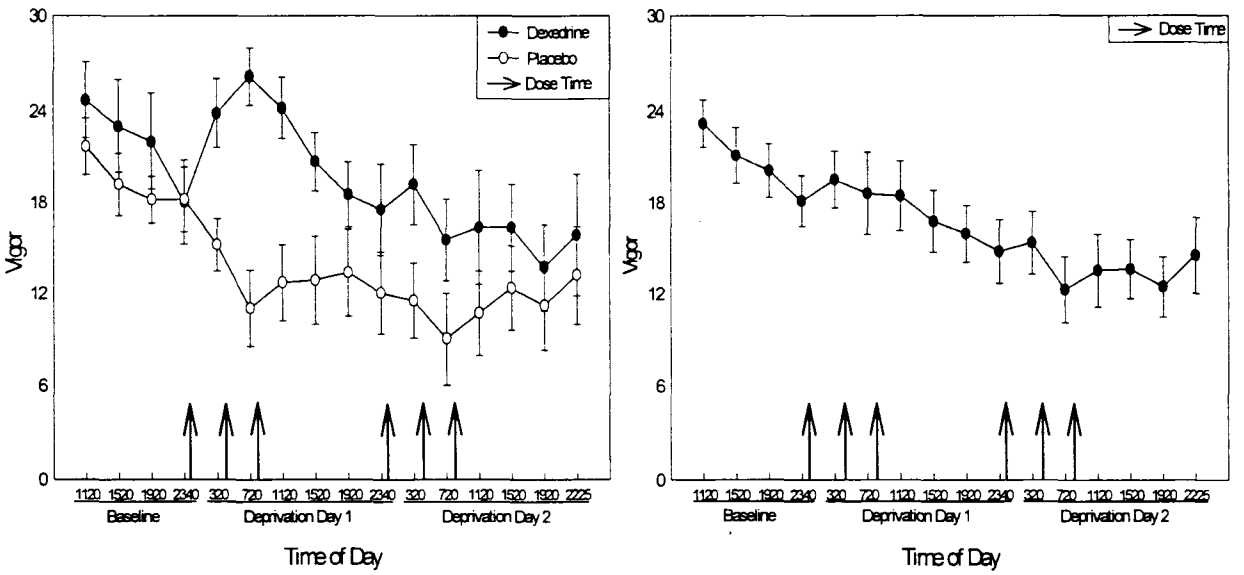

Figure 23. Effects of drug and session (left) and session with the other factors collapsed (right) on POMS vigor-activity ratings.

Fatigue-inertia scale

The 2-way ANOVA on fatigue-inertia scores, which signify weariness and tiredness, revealed an interaction between drug and session ($F(15,60)=2.12$, $p=.0211$), and main effects on the drug ($F(1,4)=8.60$, $p=.0427$) and session ($F(15,60)=17.50$, $p<.0001$) factors. As is shown in figure 24, the interaction was due to the fact that there were no differences among the drug conditions during baseline, but there were higher levels of fatigue under placebo than Dexedrine at 0720, 1120, and 1520 on the first deprivation day ($p<.05$). Fatigue also tended to be higher under placebo than Dexedrine at 2340 on this day ($p=.0557$). There were no differences between the drug conditions at later times. The drug main effect was consistent with what was observed in the drug-by-session interaction in that fatigue was generally higher under placebo than Dexedrine (the means were 6.5 versus 3.0, respectively). The overall session effect evidenced significant linear, quadratic, and cubic trends ($p<.05$) which resulted from a combination of cumulative sleep deprivation and circadian factors (see figure 24).

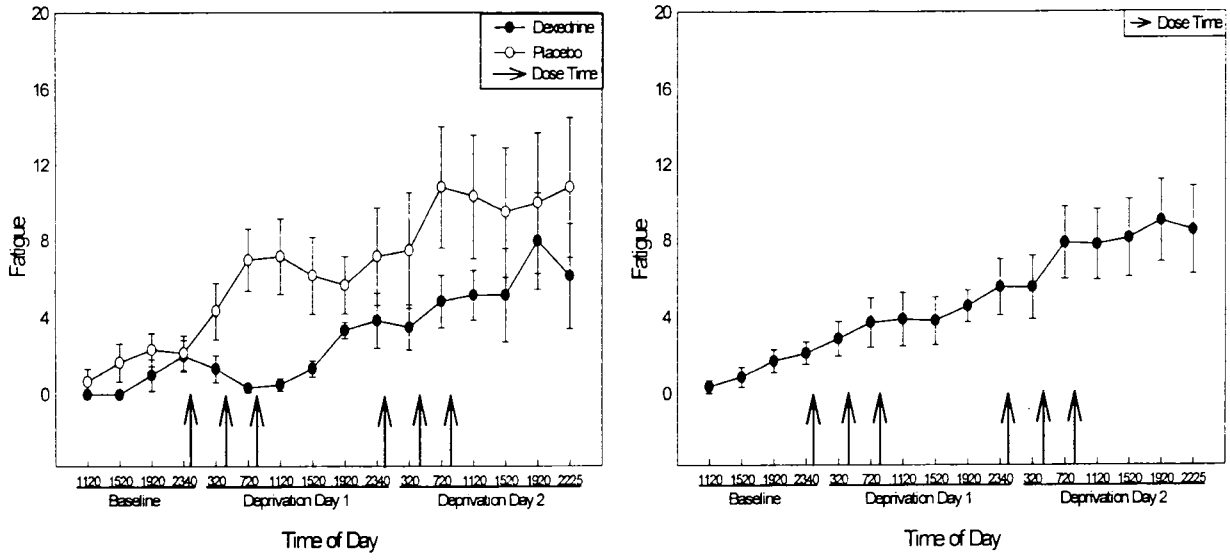

Figure 24. Effects of drug and session (left) and session with the other factors collapsed on POMS fatigue-inertia ratings.

Confusion-bewilderment scale

Analysis of the confusion-bewilderment scores, which reflect difficulties in mental abilities, showed several effects similar to those seen with the previous two scales. Specifically, there was a drug-by-session interaction ($F(15,60)=3.11$, $p=.0009$), a drug main effect ($F(1,4)=11.13$, $p=.0289$), and a session main effect ($F(15,60)=5.90$, $p<.0001$). The interaction was attributable to the lack of condition-related differences during the baseline sessions, which was followed by significantly higher confusion scores under placebo than Dexedrine at 1120, 1520, 1920, and 2340 on the first deprivation day and at 0720 and 1920 on the second deprivation day ($p \leq .05$). This drug-by-session interaction is depicted in figure 25. The drug main effect was attributable to the general increase in self-perceptions of confusion which occurred under placebo in comparison to Dexedrine (the means were 4.1 versus 2.0, respectively). The session effect was because of significant linear, cubic, and quadratic trends ($p<.05$). Figure 25 shows that these resulted from a gradual deprivation-related increase in mental confusion with circadian-related peaks at 0720 on both deprivation days; however, these trends should be cautiously interpreted in light of the significant drug-by-session interaction on confusion scores.

VAS

The VAS ratings collected during 4 baseline sessions (1120, 1520, 1920, and 2340) and 12 deprivation sessions (0320, 0720, 1120, 1520, 1920, and 2340 on deprivation day 1; and at 0320, 0720, 1120, 1520, 1920, and 2225 on deprivation day 2) under the influence of placebo versus Dexedrine were analyzed in a series of 2-way ANOVAs for drug and session. The 2340 scores and the 2225 scores for each scale were placed in the same level of the session factor for ease of analysis (the earlier test time at the end of deprivation day 2 was necessary to ensure that subjects

could initiate recovery sleep by 2300). Each of the ratings (alertness, anxiety, energy, confidence, irritability, nervousness, sleepiness, and talkativeness) was analyzed separately.

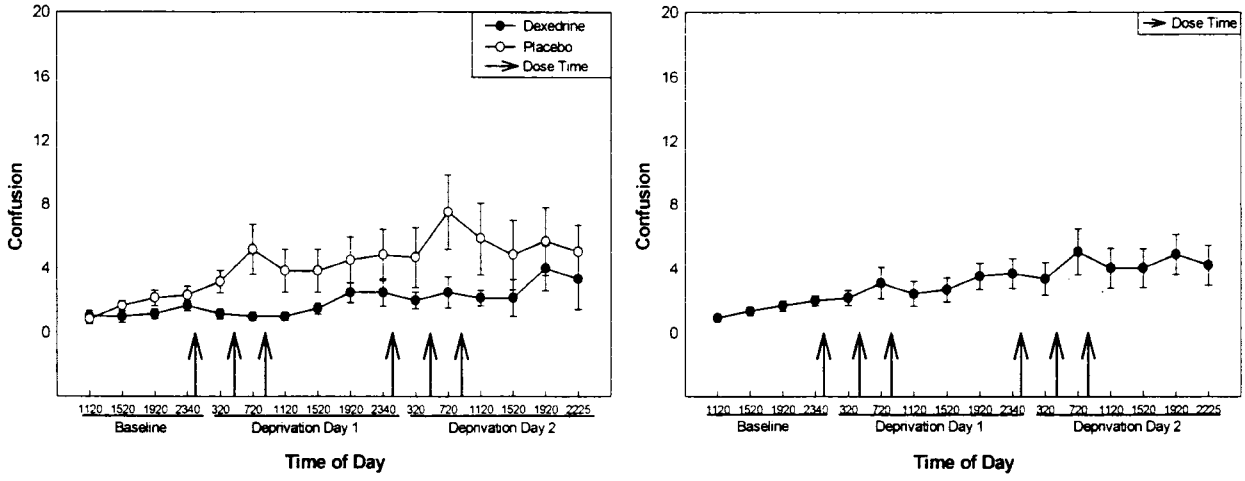

Figure 25. Effects of drug and session (left) and session with the other factors collapsed (right) on POMS confusion-bewilderment ratings.

There were significant drug-by-session effects on five of the eight VAS items. The interaction on the alertness scale ($F(15,60)=3.88$, $p=.0001$) was due to the fact that there were no differences among any of the baseline sessions, but ratings were substantially lower ($p<.05$) under placebo than Dexedrine at 0320, 0720, and 1120 on the first deprivation day and at 0720 and 1920 on the second deprivation day (there was a tendency at 1120 ($p=.0562$) as well). A similar effect was observed on the energy scale ($F(15,60)=3.36$, $p=.0004$) where analysis of simple effects indicated no differences at baseline (with the exception of the 2340 test), but substantial declines under placebo versus Dexedrine ($p<.05$) at 0320, 0720, 1120, 1520, and 1920 on the first deprivation day and at 0320 and 0720 on the second deprivation day. On the irritability scale, although there was a significant interaction ($F(15,60)=2.27$, $p=.0130$), none of the simple effects revealed differences between placebo and Dexedrine at any of the testing times. However, there appeared to be increased irritability under placebo versus Dexedrine at 0720 on both deprivation days (although it was not significant). There was a drug-by-session interaction on the sleepiness scale ($F(15,60)=2.43$, $p=.0077$) as well. Analysis of simple effects attributed this to the fact that there were no differences during the baseline, but there were marked increases in sleepiness under placebo in comparison to Dexedrine ($p<.05$) at 0720, 1120, and 1520 on the first deprivation day and at 0720 on the second deprivation day. The effects of drug and session on talkativeness ratings ($F(15,60)=4.14$, $p<.0001$) were somewhat similar to those on sleepiness in that subjects did not rate themselves differently during the baseline sessions, but felt they were less talkative ($p<.05$) under placebo than Dexedrine at 0320, 0720, and 1120 on the first deprivation day and at 0320 on the second deprivation day. One curious effect occurred on this scale, and that was the reversal of the impact of drug at 1520 where talkativeness actually was higher under placebo versus Dexedrine at this one time point (the apparently similar effect at 2225 was not significant). The drug-by-session effects for all five scales are shown in figure 26.

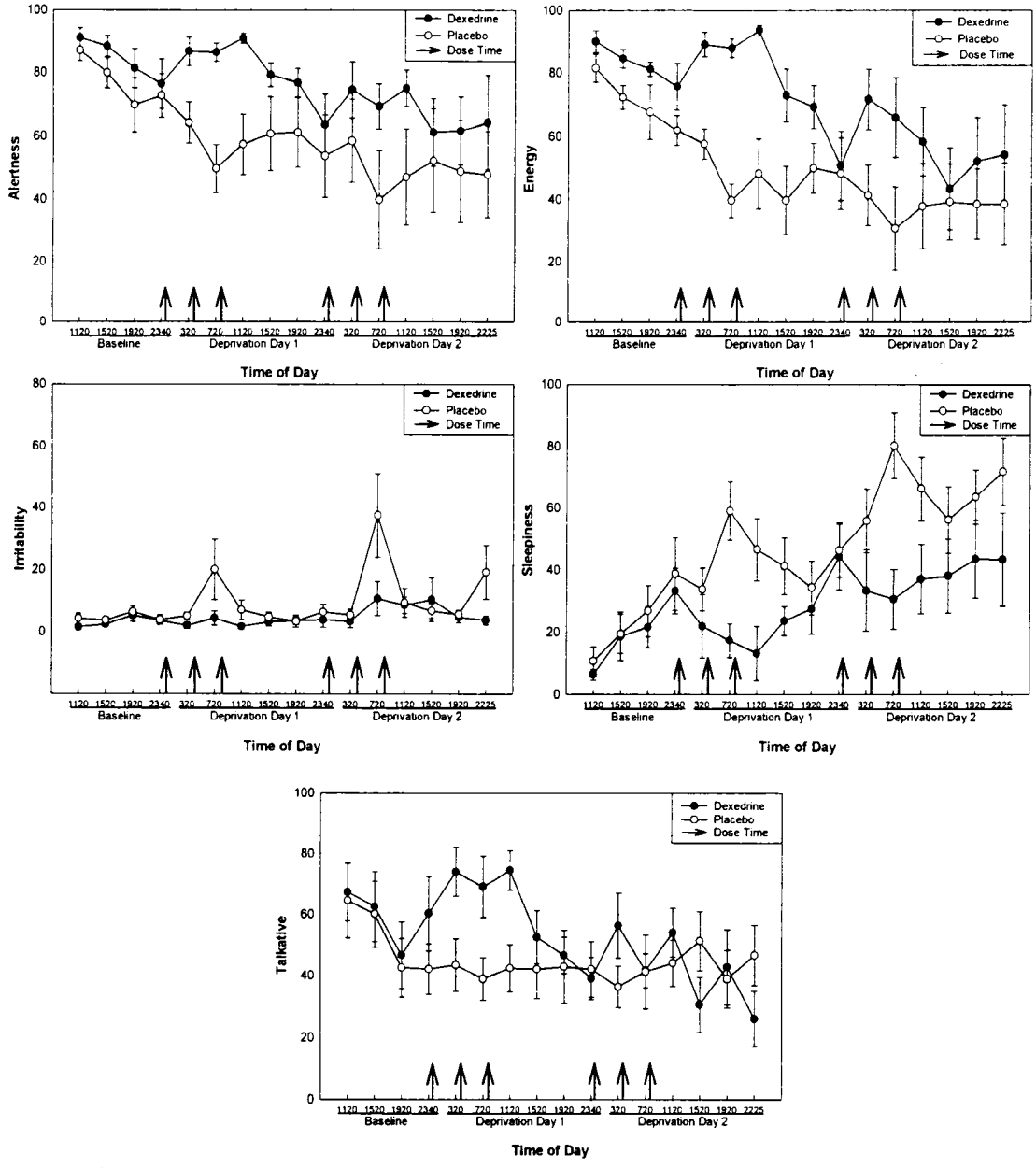

Figure 26. Effects of drug and session on VAS alertness and energy (top), irritability and sleepiness (second row), and talkativeness (bottom).

There were drug main effects on each of these five scales as well--alertness ($F(1,4)=13.59$, $p=.0211$), energy ($F(1,4)=18.44$, $p=.0127$), irritability ($F(1,4)=19.43$, $p=.0116$), sleepiness ($F(1,4)=9.80$, $p=.0352$), and talkativeness ($F(1,4)=7.73$, $p=.0498$). Examination of the overall means under placebo and Dexedrine in each case showed that subjects were less alert (59 versus 77), less energetic (50 versus 71), more irritable (9 versus 5), more sleepy (47 versus 28), and less talkative (45 versus 53) after receiving placebo. Dexedrine attenuated these effects.

There were session main effects on alertness ($F(15,60)=13.52$, $p<.0001$), energy ($F(15,60)=11.33$, $p<.0001$), confidence ($F(15,60)=3.40$, $p=.0004$), irritability ($F(15,60)=3.18$, $p=.0007$), nervousness ($F(15,60)=2.90$, $p=.0018$), sleepiness ($F(15,60)=12.75$, $p<.0001$), and talkativeness ($F(15,60)=4.45$,$p<.0001$). Trend analysis showed there were significant linear, quadratic, and cubic trends in the data from each scale ($p<.05$), with the exception of nervousness where there was no generalized increase or decrease (no linear trend) as a function of deprivation (the overall slope of the line was flat). The session effects on all of these scales should be cautiously interpreted since there were higher-order interactions on the majority of them; however, generally speaking, there were gradual declines in alertness, energy, confidence, and talkativeness as deprivation progressed. At the same time, irritability and sleepiness increased. In every case, the influence of circadian rhythms could be seen as subjects reported the most problems at 0720 on both deprivation days, with a slight recovery in between these two time points, and once again following the 0720 test on the second deprivation day (see figure 27).

MATB

The speed and accuracy with which subjects completed the MATB at 3 baseline (0330, 0730, and 1130) and 10 deprivation times (0330, 0730, 1130, 1530, and 1930 on deprivation day 1; and 0330, 0730, 1130, 1530, and 1930 on deprivation day 2) under the influence of placebo versus Dexedrine were analyzed with 2-way ANOVAs. Each task (communications, resources management, systems monitoring, and tracking) was analyzed separately.

Communications

Three variables from this subtask were analyzed. The first was the RT from when subjects were given an instruction to "change a communications radio frequency" until when they actually changed the frequency. The second was the standard deviation of these reaction times (SDRT). The third was time out (TO) errors, or the number of times subjects failed to respond to an instruction to change a radio frequency. There were no drug-by-session interactions, but there were main effects on the session factor for RT ($F(12,48)=3.23$, $p=.0019$), SDRT ($F(12,48)=3.59$, $p=.0008$), and TO errors ($F(12,48)=5.76$, $p<.0001$). Trend analysis revealed significant quadratic and cubic trends for the RT data ($p<.05$) which were due to the fact that RT was relatively short during baseline, increased at 0730 on the first deprivation day, dropped until 0330 and 0730 the next day (at which time it peaked), and then decreased again afterwards. SDRT behaved similarly to RT, but in this case, all three trends were significant ($p<.05$), despite the fact that the linear effect is not especially noticeable. For TO errors, there also were significant linear, quadratic, and cubic trends which resulted first from the gradual increase in TO errors as the deprivation period progressed and second from the circadian effects which served to produce substantially greater TO errors at 0730 on both of the deprivation days. All of these session effects are depicted in figure 28.

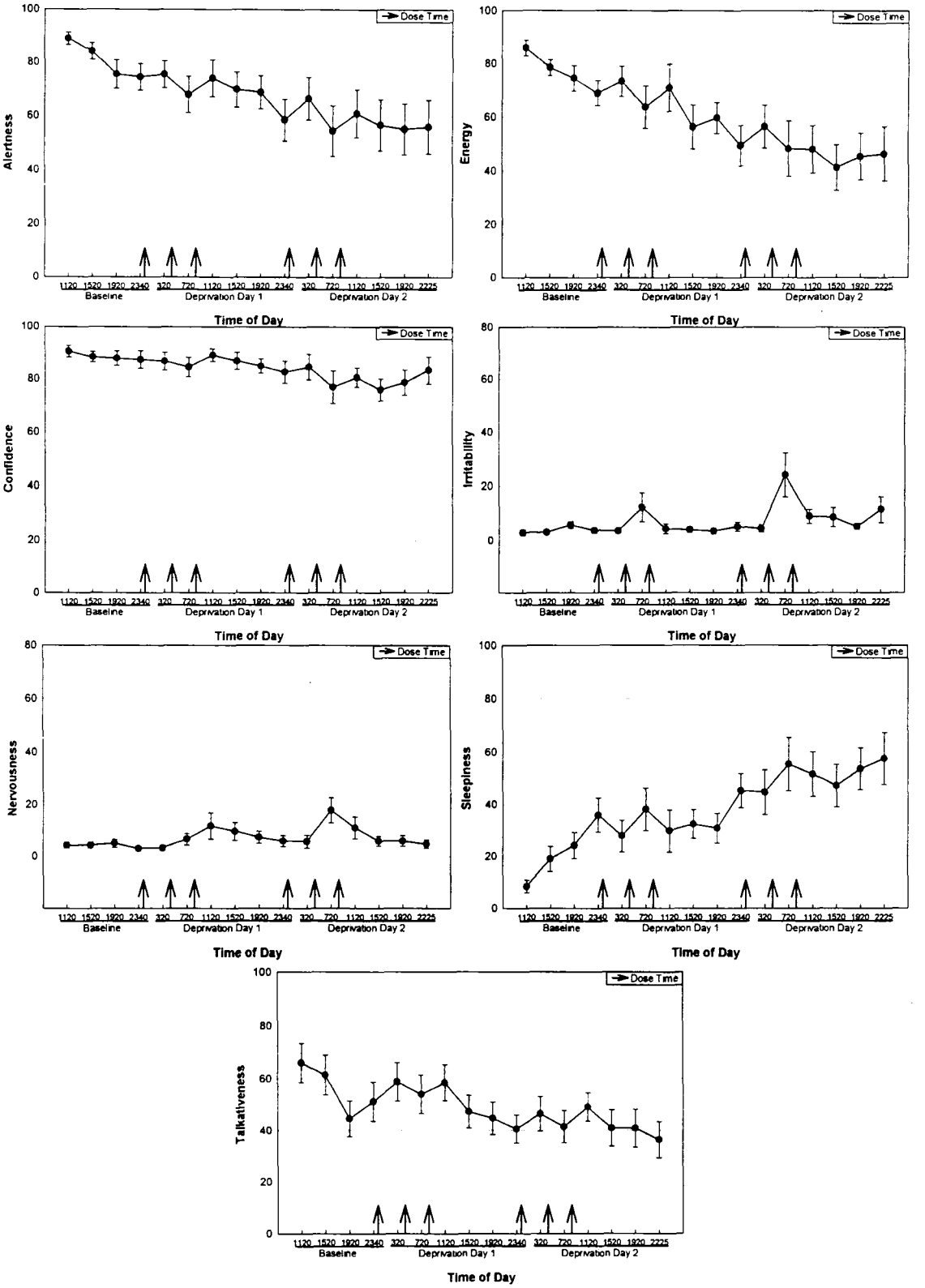

Figure 27. Effect of session (with the other factors collapsed) on VAS ratings.

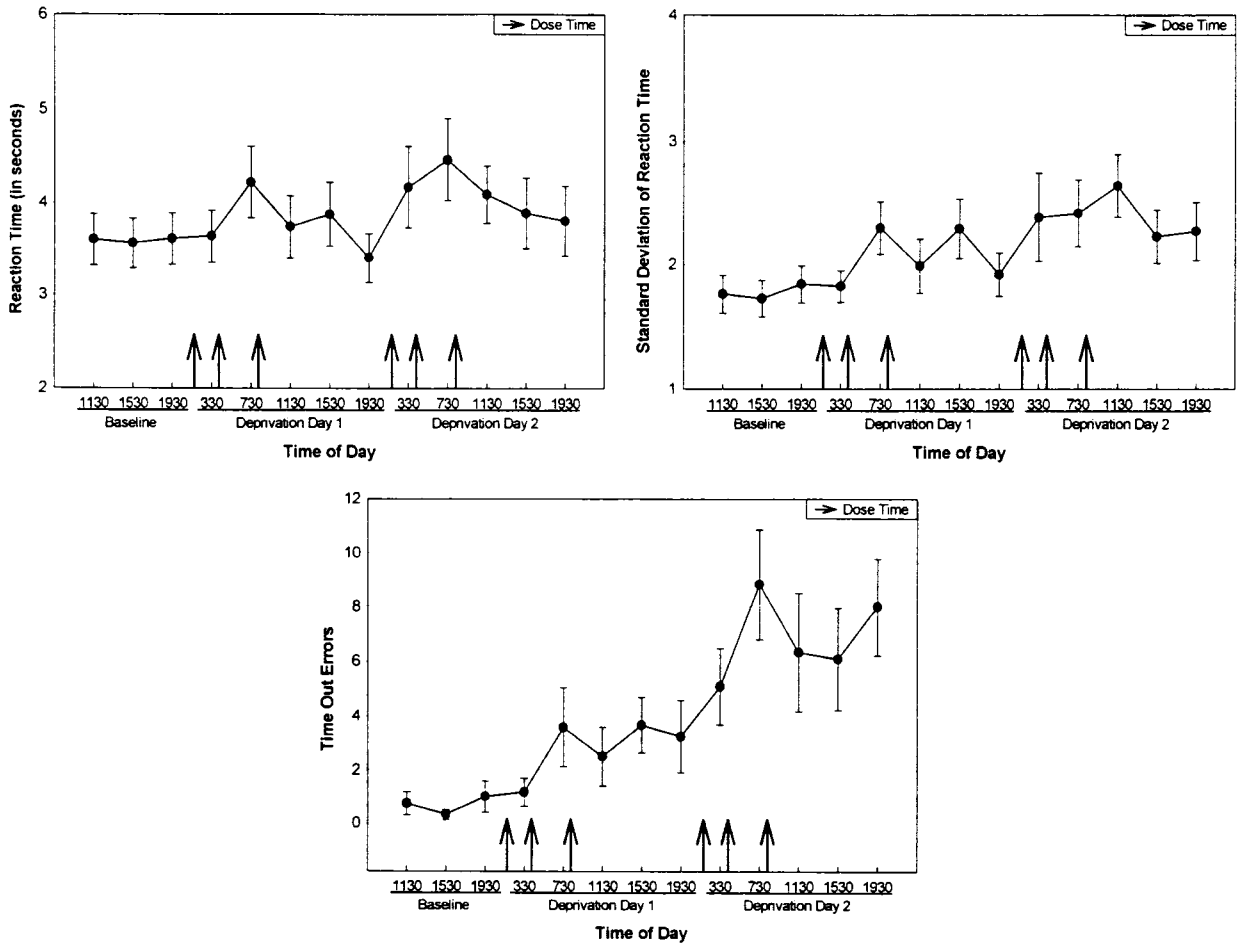

Figure 28. Effect of session on reaction time for correct responses (top left), standard deviation of RT (top right), and time out errors (bottom) in MATB communications.

Resource management

One variable from this task was analyzed. This was a measure of the accuracy with which subjects were able to maintain "fuel levels in their fuel tanks" at the ideal value of 2500 units (mean deviation of tanks A and B from 2500). The ANOVA on these data revealed no significant interactions or main effects.

Systems monitoring

Six variables from this subtask were analyzed. The first was RT to lights which indicated how long it took subjects to respond to the onset of one light with a key press or the extinguishing of another light with a different key press. The second was SDRT for lights. The third was RT to dials which indicated how long it took for subjects to enter a key press in response to an out-of-limits excursion of any of four dials. The fourth was SDRT for dials. The fifth and sixth variables were TO errors for lights and TO errors for dials. The ANOVA on these data showed there were drug-by-session interactions on RT to lights ($F(12,48)=3.37$, $p=.0013$)

and dials (F(12,48)=3.35, p=.0014), and TO errors to lights (F(12,48)=2.61, p=.0092), and dials (F(12,48)=3.32, p=.0015). Analysis of simple effects indicated that there were no differences between the Dexedrine and placebo baseline sessions on any of the four variables. Instead, all of the drug-related effects occurred later during the deprivation period. RT to lights was significantly slower under placebo versus Dexedrine at 0330 on the first deprivation day and at 0330, 0730, 1130, and 1530 on the second deprivation day. RT to dials was slower under placebo at 1130 and 1530 on the first deprivation day and at 0730, 1130, and 1730 on the second deprivation day. These RT differences are depicted in figure 29. TO errors for both lights and dials were not affected by drug condition on the first deprivation day, but were more numerous under placebo than Dexedrine at 0730 on the second deprivation day (the effect for dials was marginally significant at p=.06). Also, TO errors to dials were more numerous under placebo than Dexedrine at 1530. These TO effects are shown in figure 29.

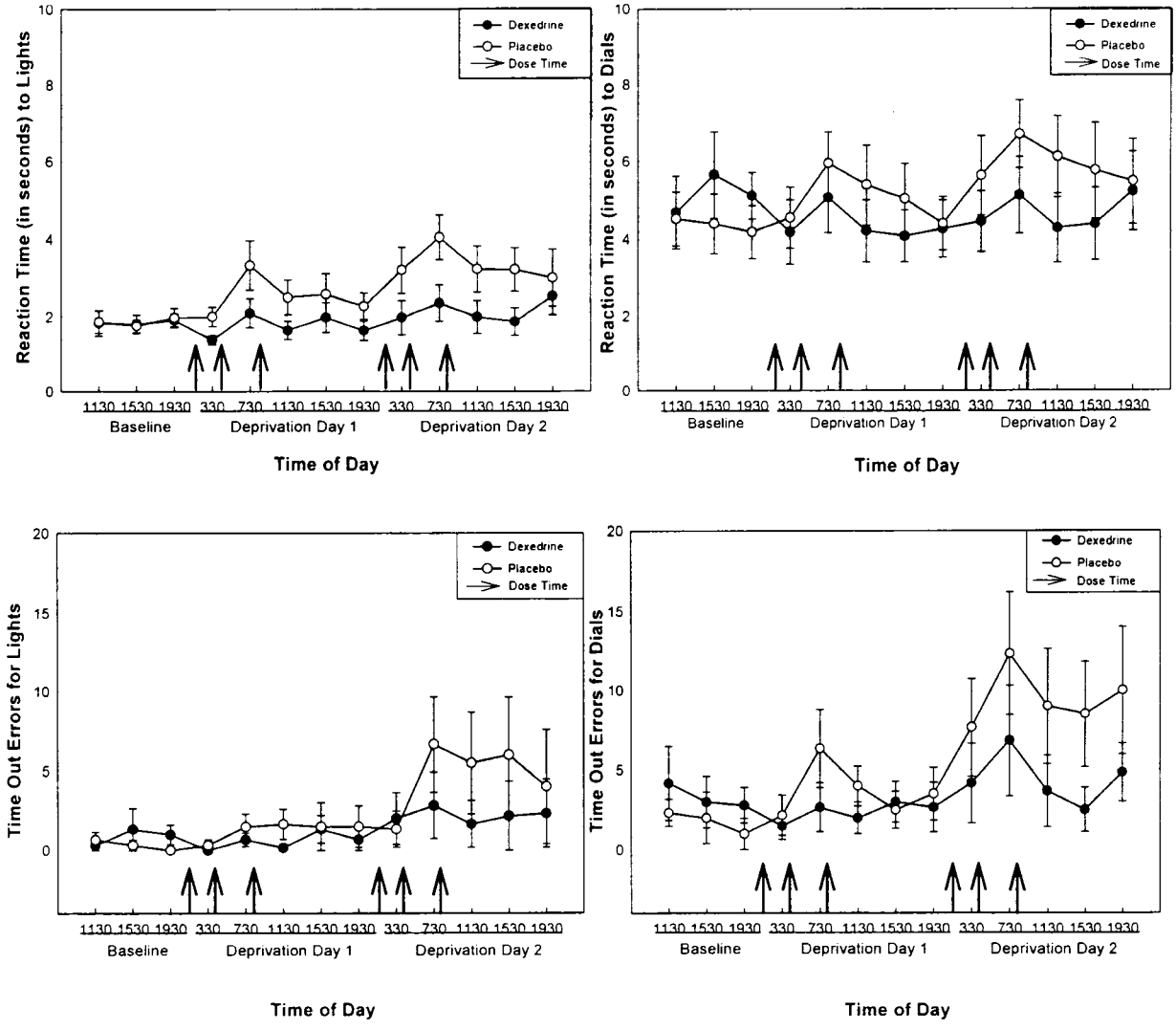

Figure 29. Effects of drug and session on reaction times to lights and dials (top) and time outs for lights and dials (bottom) on the MATB systems montioring task.

There were significant main effects on the drug factor for RT to lights ($F(1,4)=24.70$, $p=.0077$), RT to dials ($F(1,4)=9.25$, $p=.0384$), and TO errors for dials ($F(1,4)=11.62$, $p=.0271$). In addition, there was a drug main effect on SDRT to lights ($F(1,4)=23.71$, $p=.0082$). In each of these cases, performance was slower, more variable, or less vigilant under placebo in comparison to Dexedrine. There were significant main effects on the session factor for RT to lights ($F(12,48)=6.66$, $p<.0001$), RT to dials ($F(12,48)=2.74$, $p=.0066$), SDRT for lights ($F(12,48)=4.31$, $p=.0001$), TO errors for lights ($F(12,48)=2.38$, $p=.0168$) and TO errors for dials ($F(12,48)=5.15$, $p<.0001$). Most of these appeared to be largely the result of performance decrements that occurred under the placebo condition which affected the overall session means. Trend analysis indicated there was a significant linear, quadratic, and cubic trend ($p<.05$) for RT and SDRT to lights. In both cases, there was a decrease in performance (i.e., increased RT and variability) as the deprivation period increased, as well as a circadian effect which especially impaired performance at 0730 on both of the deprivation days. For RT to dials, there was no linear trend, but there were significant quadratic and cubic trends ($p<.05$) due to the same type of circadian effect found with RT and SDRT for lights. There was only a significant linear trend ($p<.05$) and a marginally-significant cubic trend ($p=.0576$) on TO errors for dials. These were because time out errors gradually increased as a function of deprivation, but after a sharp peak at 0730 on the second deprivation day, the time out errors declined. Trend analysis on TO errors for lights revealed that none of the three trends analyzed here turned out to be significant, probably because the session effect on this variable was not as pronounced as it was on the others. The session main effects on the systems monitoring task are shown graphically in figure 30.

Tracking. Only one variable from the tracking task was analyzed, and this was the root mean square (RMS) error or the amount of deviation from where the subject was supposed to be holding the cursor on the target to where he/she actually held the cursor. The ANOVA on RMS errors indicated there was a drug-by-session interaction ($F(12,48)=8.26$, $p<.0001$). The analysis of simple effects attributed this interaction to the fact that tracking performance was the same during the placebo and Dexedrine baselines, but deteriorated rapidly afterwards under the placebo condition while Dexedrine attenuated this effect. At every session during the deprivation period (with the exception of 0330 and 1930 on the first day), tracking accuracy was impaired under placebo relative to Dexedrine. In addition, RMS tracking errors tended to be greater under placebo than Dexedrine at the two outstanding sessions, 0330 and 1930 ($p=.0587$) as can be seen in figure 31 (first panel).

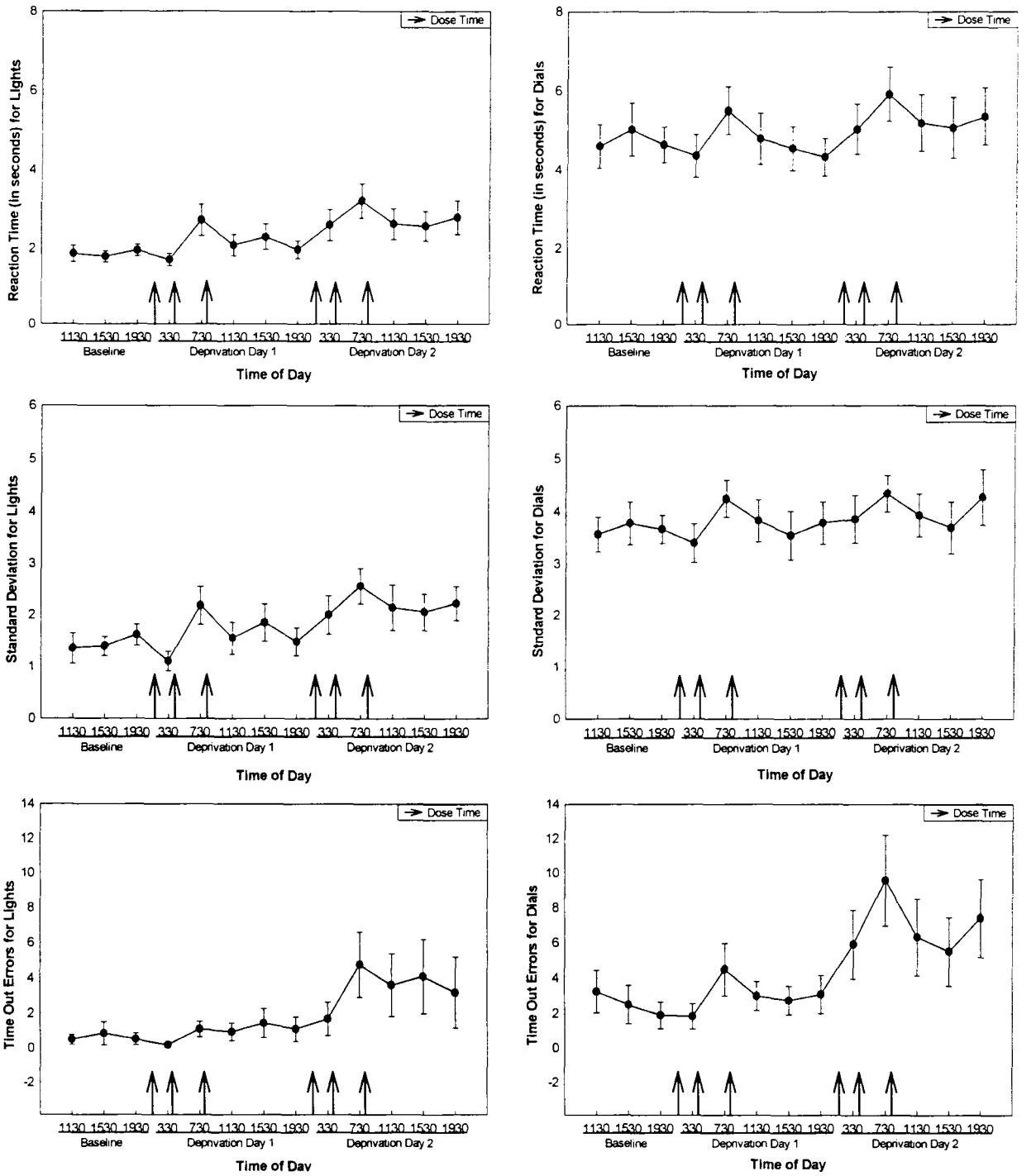

Figure 30. Effect of session on reaction times (top), standard deviation of reaction times (middle), and time out errors (bottom) in the MATB systems monitoring task.

There were drug ($F(1,4)=34.08$, $p=.0043$) and session ($F(12,48)=16.83$, $p<.0001$) main effects as well. The drug main effect was because of larger overall tracking errors under placebo than Dexedrine. The session main effect was due to linear, quadratic, and cubic trends in the

data (p<.05) which resulted from a gradual increase in tracking errors from baseline until the end of deprivation, as well as a strong circadian effect which impaired tracking performance more than usual at 0730 on both of the deprivation days (see figure 31, second panel). Note that most of the performance impairments across sessions were due to averaging placebo-related decrements with the relatively stable tracking behavior observed under Dexedrine.

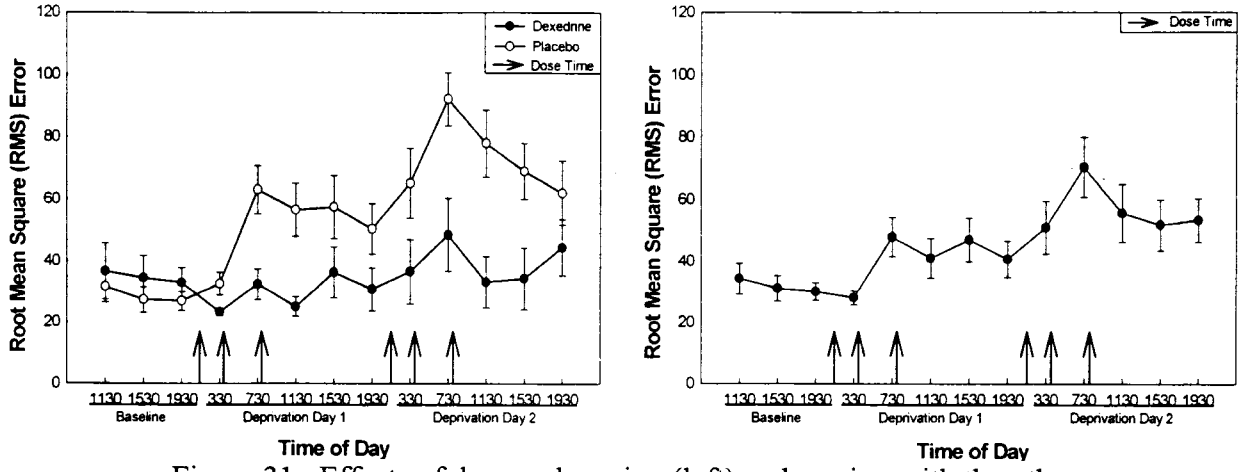

Figure 31. Effects of drug and session (left) and session with the other factors collapsed (right) on the MATB tracking task.

Vital signs data

Measures of temperature, pulse, and blood pressure were collected several times during baseline and throughout each 64-hour deprivation period. These data were gathered primarily to monitor the safety and well-being of research participants; however, they will be analyzed and presented here to fully explore the impact of sleep deprivation and Dexedrine on human subjects. These data were analyzed in a series of 2-way ANOVAs for drug (placebo vs. Dexedrine) and time (there were 10 baseline times and 25 deprivation times). Note that some of the oral temperature data were confounded by the fact that subjects periodically ate or drank hot/cold substances within 5 minutes of data collection. Steps were taken to minimize this problem, but because of constraints in the testing schedule (sometimes subjects had only 10 minutes between tests), it was virtually impossible to avoid some contamination of oral temperature readings. The other measures should, however, be accurate.

Oral temperature

There were no drug-related effects on oral temperature, but there was a session main effect ($F(34,136)=3.75$, $p<.0001$). Although no posthoc analyses were conducted due to the large number of comparisons that would have been involved, it is clear that the time effect was because of circadian variations in body temperature. Temperature readings were lowest in the early morninings (at about 0800) and highest in the afternoons and early evenings (see figure 32, first panel). Although there were no significant drug effects, the data are partitioned by Dexedrine and placebo for informational purposes.

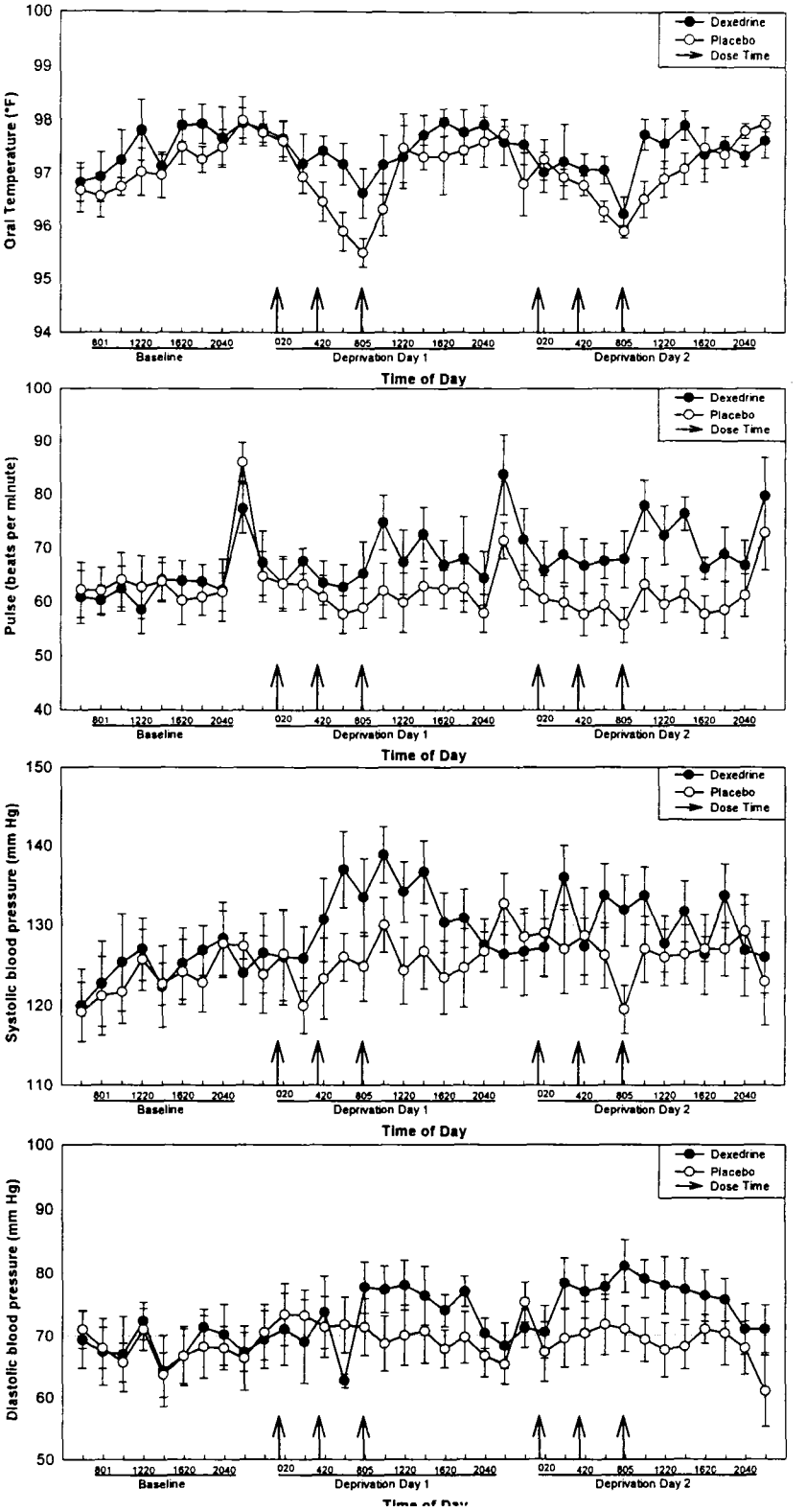

Figure 32. Effects of drug and session on temperature, pulse, and blood pressure.

Pulse

The ANOVA of pulse data indicated a significant drug-by-time effect ($F(34,136)=2.66$, $p<.0001$), a drug main effect ($F(1,4)=22.48$, $p=.0090$), and a time main effect ($F(34,136)=5.93$, $p<.0001$). Analysis of simple effects showed that pulse rate was not different between the two conditions at any of the baseline sessions (pre-drug); however, there was a marginally significant ($p=.0562$) increase in pulse under Dexedrine at 1010 and a significant increase ($p\leq.05$) in pulse under Dexedrine versus placebo at 1410 on the first deprivation day. Pulse rate was again higher under Dexedrine than placebo at 0420, 0610, 0805, 1010, 1220, 1410, 1620, and 1820 on the second deprivation day (see figure 32, second panel). These changes were responsible for the overall drug main effect which occurred because pulse rates were generally higher under Dexedrine than placebo (the means were 68 beats per min. versus 62 beats per min.). The session main effect was not pursued further with posthoc analyses because of the number of comparisons that would have been involved and the fact that this effect holds no informational value in light of the higher-order interaction already discussed.

Systolic blood pressure

There was a drug-by-time interaction ($F(34,136)=1.69$, $p=.0193$) on the systolic blood pressure readings which analysis of simple effects revealed was due to the lack of a difference between the two conditions at baseline (predrug), which was followed by a general increase under Dexedrine versus placebo later. Specifically, blood pressure was higher under Dexedrine than placebo at 0610, 0805, 1010, 1220, and 1410 on the first day of deprivation and at 0210, 0610, and 0805 on the second day of deprivation ($p\leq.05$). These differences are shown in figure 32 (third panel). There was a drug main effect attributable to an overall elevation in blood pressure with Dexedrine versus placebo (the means were 129 mmHg versus 125 mmHg), and a time main effect ($F(34,136)=2.12$, $p=.0013$) which was not pursued further for reasons already discussed.

Diastolic blood pressure

There was a drug-by-time interaction ($F(34,136)=1.56$, $p=.0384$) on the diastolic blood pressures which was due to the absence of any condition-related differences at baseline (predrug) followed by slight but consistent elevations later in the deprivation period. Diastolic pressure was higher under Dexedrine than placebo ($p\leq.05$) at 0805, 1010, 1220, 1810, and 2040 on the first deprivation day and at 0210, 0805, 1010, 1220, 1410, and 2220 on the second deprivation day (see figure 32, fourth panel). There was a drug main effect ($F(1,4)=12.65$, $p=.0237$) because of higher overall blood pressure under Dexedrine in comparison to placebo (73 mmHg versus 69 mmHg) and a time main effect ($F(34,136)=2.28$, $p=.0005$) which was not pursued further with posthoc analyses.

Polysomnographic data

The data from the baseline sleep night as well as the first recovery nights following the Dexedrine days and the placebo days were analyzed with a one-way ANOVA with repeated measures. The second recovery night from the first sleep deprivation period was not analyzed since a second recovery night was not recorded following the second sleep deprivation period. The number of minutes from lights out to the appearance of stage 2 sleep (sleep onset); the percentage of time subjects spent in sleep stages 1, 2, 3, 4, and rapid eye movement (REM); the percentage of time subjects were awake after sleep onset; sleep efficiency (defined as total sleep time divided by time in bed); REM latency (defined as the time from sleep onset to the first REM period of at least 2 minutes in duration); and movement time were the variables of interest. Prior to the analysis, the percent data were converted using the two arcsine square-root transformation to stabilize the variances.

The analysis revealed significant differences among the days for sleep onset ($F(2,10)=15.65$, $p=.0008$), with a longer sleep onset on baseline than on either of the recovery nights. The two recovery days were not significantly different from each other. Sleep efficiency was significantly different among the nights ($F(2,10)=61.50$, $p<.0001$), with subjects having better sleep efficiency during the two recovery nights than during the baseline night, and better sleep efficiency during the placebo recovery night than during the Dexedrine recovery night ($p<.05$). These effects are shown in Figure 33.

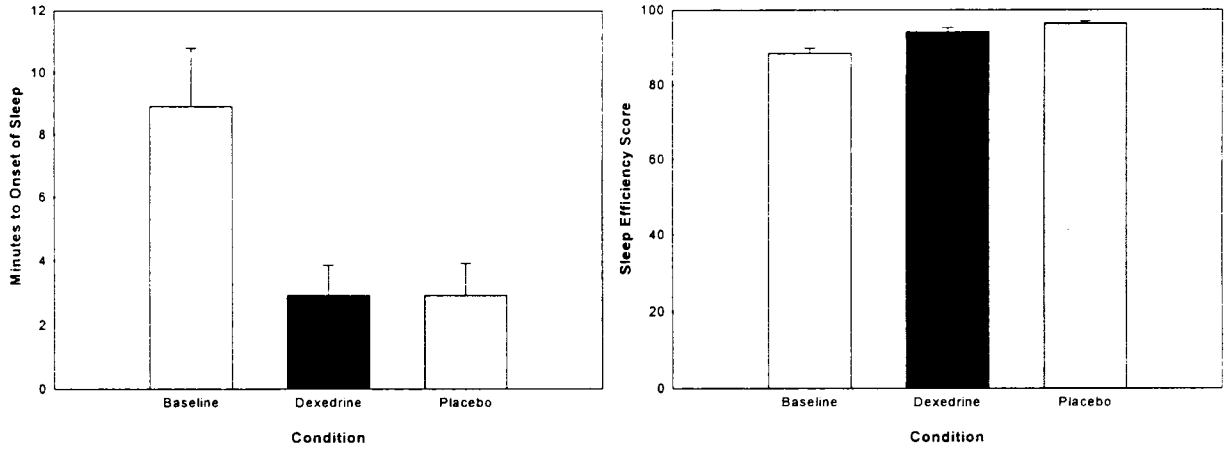

Figure 33. Effect of Dexedrine and placebo on latency to sleep onset (left) and sleep efficiency (right).

There was also a difference among the days for the percentage of time spent in stage 1 sleep ($F(2,10)=41.28$, $p<.0001$), stage 3 sleep ($F(2,10)=9.37$, $p=.0051$), stage 4 sleep ($F(2,10)=4.82$, $p=.0342$), and stage REM sleep ($F(2,10)=11.34$, $p=.0027$). Comparisons among the means indicated that there was more stage 1 sleep during baseline than during both recovery nights, and more stage 1 during the Dexedrine recovery night than during the placebo recovery night. There was less stage 3 sleep during the baseline night than during the Dexedrine recovery night and more stage 3 during the Dexedrine recovery night than during the placebo recovery night;

however, there was no difference between the baseline and placebo recovery night. There was less stage 4 sleep during the baseline night than during the Dexedrine recovery night, but no differences elsewhere. No difference occurred between the baseline night and the two recovery nights for REM sleep, but there was significantly more REM sleep during the placebo recovery night than during the Dexedrine recovery night. These effects are shown in figure 34.

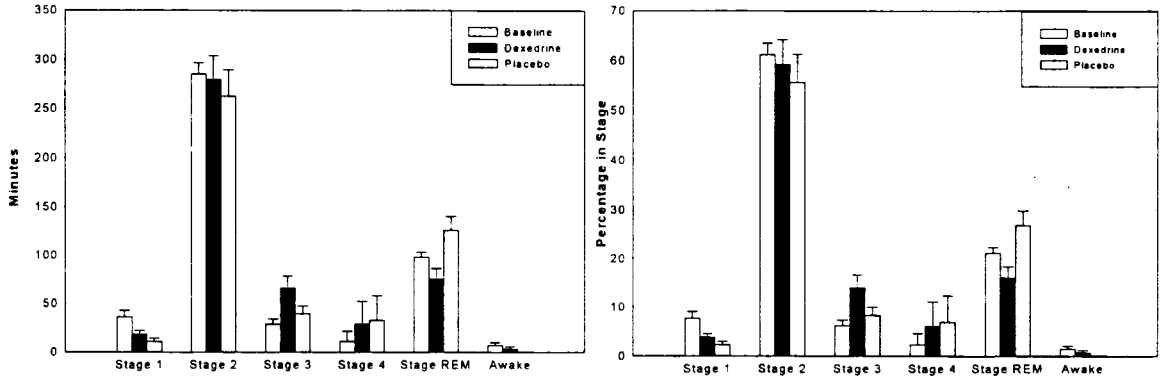

Figure 34. Effects of Dexedrine and placebo on sleep architecture (minutes in each stage and percentage of each stage).

REM latency was different among the days ($F(2,10)=18.52$, $p=.0004$) with a longer latency to REM sleep during the Dexedrine recovery night than during either the baseline night or the placebo recovery night. The latency to REM sleep also was longer during the baseline night than during the placebo recovery night (see figure 35).

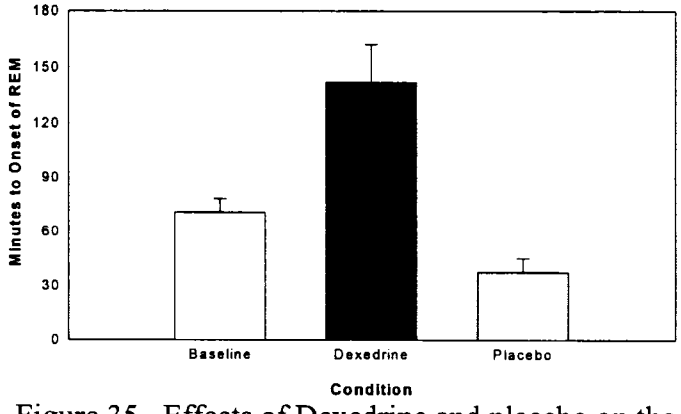

Figure 35. Effects of Dexedrine and placebo on the latency to REM sleep onset.

Discussion

This investigation was conducted to extend the findings of earlier studies which indicated Dexedrine was efficacious for safely maintaining the performance and alertness of pilots throughout 40-hour periods of continuous wakefulness. Prophylactic adminstration of Dexedrine previously had been proven especially beneficial for attenuating the impact of sleep loss on flight

performance and mood after subjects had been awake continuously for 20 to 29 hours (from 0300-1200) during 40 hours of sustained operations (there were often differences later on as well). In these studies, 10-mg doses of Dexedrine were administered prior to observed deteriorations in performance in an effort to prevent decrements from occurring in the first place, rather than to restore already deteriorated performance to predeprivation levels. This strategy was effective in the short term (40-hours). The present study examined whether or not Dexedrine administered in a similar fashion would be capable of sustaining performance and alertness beyond 40 hours, for up to 64 hours without sleep. Based on a number of indices, it is clear that Dexedrine is in fact useful for preserving aviator skill for more prolonged periods.

Flight performance

In this study, the flight performance of sleep-deprived pilots was effectively maintained by Dexedrine for up to 58 hours (the last flight of the investigation). Meanwhile, performance under placebo deteriorated significantly.

The present findings supported those from our earlier 40-hour studies (Caldwell et al., 1995; Caldwell et al., 1996; and Caldwell and Caldwell, 1997) in that Dexedrine sustained flight performance relative to placebo most reliably at 0500 and 0900 on the first deprivation day (after 22-27 hours awake). These are the two flights that fell within the time bracket when alertness has been shown to suffer the most (0800 was the low point for oral temperatures on the deprivation days in this study), and these are the two that deteriorated most substantially under placebo. There often were similar (Dexedrine-better-than-placebo) effects later in this first deprivation period as well.

In the second deprivation period (beyond the first 40 hours of wakefulness), Dexedrine continued to significantly attenuate the performance reductions observed under placebo on two of the six maneuvers as early as 0100 on the second deprivation day (after 42 hours awake), on four of the flight maneuvers at 0500 (after 46 hours awake), on 4 of the maneuvers at 1300 (after 54 hours awake), and on one maneuver at 1700 (after 58 hours awake).

Analysis of flight performance as a function of deprivation generally showed declines under placebo from the 0500 flight on the first deprivation day through the 1700 flight on the second deprivation day, whereas performance under Dexedrine essentially was preserved at baseline levels. In every instance where there were statistically-significant drug effects, performance under Dexedrine was superior to performance under placebo 100 percent of the time, and no reversals of this relationship were observed. A maneuver-by-maneuver examination of the data showed that Dexedrine effectively sustained performance at predeprivation levels throughout most of the flight profile, while flight performance under placebo deteriorated in every instance.

These findings, that repeated prophylactic 10-mg doses of Dexedrine could sustain performance at baseline levels throughout a 64-hour period of continuous wakefulness, extend those of Pigeau et al. (1995) who reported that widely spaced 20-mg doses were effective for attenuating initial performance declines and for recovering already degraded performance. Reducing the quantity of each dose and shortening the dose interval (as was done in this

investigation) prevented the deprivation-related declines and did not produce unwanted side effects.

MATB and desktop simulator tasks

Although two of the subtests from the MATB and the primary desktop-flight-simulation task were unaffected by the placebo/Dexedrine conditions, the other tests generally yielded data consistent with the flight performance outcomes. The subjects' abilities to respond quickly to incoming information was better under Dexedrine than placebo, especially during the later parts of the periods of sustained wakefulness. This was evidenced by faster RTs to MATB warning lights and dial excursions under Dexedrine than placebo on both the first and second deprivation days. The averaged RTs tended to remain relatively constant throughout 64 hours of continuous wakefulness under Dexedrine, whereas response speed progressively slowed due to increased sleepiness under placebo. Statistically-significant impairments under placebo (relative to Dexedrine) were observed as early as 21 hours without sleep on RT to lights and 28 hours without sleep on RT to dials. A similar effect was seen in the RTs to the secondary task in the desktop flight simulator (although the differences appeared later). Responses to target tones degraded significantly under placebo versus Dexedrine after 47 and 51 hours of continuous wakefulness. Vigilance likewise was adversely affected by fatigue under placebo, whereas Dexedrine preserved attentional resources. This was indicated by fewer time-out errors on systems monitoring in the MATB (after 48 hours without sleep) and fewer missed target tones during the desktop simulation task (first, at the test conducted after 23 hours without sleep, and then again at the sessions completed after 47 hours without sleep). Psychomotor performance was compromised by sleepiness early in the study and throughout the deprivation period under placebo, whereas Dexedrine prevented or attenuated this problem. Tracking deviations on the MATB remained at near baseline levels throughout most of the 64-hour period when Dexedrine was administered (with 2 exceptions), but marked errors occurred under placebo as early as 24 hours into the deprivation cycle. During the test conducted after 48 hours without sleep, the magnitude of tracking errors doubled under the placebo condition relative to the Dexedrine condition.

Taken together, these performance data show that when subjects were given placebo during prolonged periods of wakefulness, they were slower to respond to problem situations, less able to identify problems requiring a response, and less accurate in performing the task at hand in comparison to when they were administered Dexedrine. These effects consistently manifested themselves after only 22 hours of sustained wakefulness and were most noticeable between 0500 and 1200 on both deprivation days (the times at which performance under placebo suffered the most, probably due to circadian effects). These were the same times at which the differences between Dexedrine and placebo were most apparent in the flight data.

Physiological indices of fatigue/alertness

A generalized slowing of central nervous system (CNS) activity, which occurred as a function of sleep loss especially under the placebo condition, no doubt produced many of the performance decrements. Although there were numerous deprivation-related changes in the

brain activity of subjects, the most pronounced were observed in the delta and theta bands. This is not surprising in light of the fact that slow-wave EEG activity is known to increase as a function of sleepiness and fatigue (Pigeau, Heslegrave, and Angus, 1987). Both delta and theta activity, normally predominant only during sleep, was elevated significantly under the placebo condition relative to Dexedrine after 23 hours of continuous wakefulness. Under the placebo condition, both types of EEG activity then continued a marked increase throughout 55 hours (and sometimes 59 hours) of deprivation. Under Dexedrine, the increase either was absent or the slope was noticeably reduced.

The fact that theta activity (and often delta activity) was significantly greater under placebo than Dexedrine at 0615, 1015, and 1415 on the first deprivation day and at 0215, 1015, and 1415 on the second deprivation day probably explains the condition-related differences in flight performance which were most apparent at 0500, 0900, and 1300 on both deprivation days (after 22-26 and 42-46 hours without sleep). Clearly, there was a slowing of CNS activity at these times, and this translated into inferior flight control in the simulator, as well as slower reaction times, decreased vigilance, and haphazard psychomotor tracking in the MATB, and inattention during the secondary task from the desktop simulation.

Self-reported mood and sleepiness

Deteriorations occurred in self-reported mood and alertness ratings throughout the 64-hours of sustained wakefulness regardless of whether drug or placebo was administered. However, administration of Dexedrine clearly attenuated these declines. Ratings of vigor, alertness, energy, and talkativeness all decayed more sharply and ratings of fatigue, confusion, and sleepiness all increased more rapidly as a function of sleep deprivation in the placebo condition than in the Dexedrine condition. Drug-related differences appeared early in the deprivation cycle as evidenced by the fact that vigor, alertness, and energy began to deteriorate after 20 hours without sleep under placebo. At this same time, these measures actually improved under Dexedrine. The decline under placebo (absent under Dexedrine) continued for at least another 4 hours at which time there was a leveling off, which was followed by a slight recovery in the afternoon of the first day. During the second deprivation day, a similar trend was observed in which self-ratings declined most notably at the session occurring after 48 hours of continuous wakefulness under placebo, whereas ratings again improved under Dexedrine. The drug-related differences in fatigue, confusion, and sleepiness began about 4 hours later than the ones for vigor, alertness, and energy, but the basic pattern of drug-by-time effects was similar.

It is noteworthy that, despite the inability of Dexedrine to fully arrest the *perceived* decrements in vigor, alertness, and energy, the performance capabilities of aviators (i.e., the simulator flights, MATB, and the secondary task from the desktop simulation) were sustained by Dexedrine at a relatively constant level throughout 64 hours of continuous wakefulness. These findings are similar to those reported by Newhouse et al. (1989). The absence of parallel declines in both data sets suggests subjects were aware of the deprivation-related impairments in overall functioning even under Dexedrine, but this did not detract substantially from their actual response capacity. This is interesting considering the widely held opinion that amphetamine administration produces inaccurate self-estimations and overconfidence in users. In this study,

there was no evidence that participants failed to appreciate the adverse affects of sleep loss on their overall status even under Dexedrine despite the fact that actual performance deteriorations were minimized by the drug. In fact, self-ratings of confidence (measured with the VAS) revealed no differences as a function of whether subjects received Dexedrine or placebo. Thus, Dexedrine did not lead to inaccurate self-perceptions or wreckless overconfidence, a finding which corroborates the results of other investigators (Higgins et al., 1975; Baranski and Pigeau, 1997).

Another point about the effects of Dexedrine versus placebo on the mood states of sleep-deprived personnel concerns the self-ratings of anger-hostility and irritability. Subjects clearly felt angry and irritable under placebo whereas they did not under Dexedrine, and this is cause for concern in the operational environment where personnel are dependent upon one another for information, task coordination, and peer support. Especially in the early morning hours of prolonged work schedules, an adverse impact on unit cohesiveness, cockpit crew coordination, and leadership can be expected because of flaring tempers and oversensitive personnel. Dexedrine appears useful for minimizing these problems.

Generally speaking, the decreased self-perceptions of alertness, energy, and vigor in combination with increased fatigue, confusion, and sleepiness under placebo relative to Dexedrine are consistent with the performance and EEG changes observed in the present context. Although the drug did not completely ameliorate the adverse impact of continuous wakefulness on mood, it was clear that Dexedrine attenuated subjective impressions of distress. This effect would offer a substantial benefit in real-world sustained operations, especially since Dexedrine-related reductions in fatigue-induced anger, hostility, and irritability should improve effective communications, peer/leader relationships, and unit efficiency in contexts where prolonged periods of sleep loss are unavoidable.

Recovery sleep

Recovery sleep was altered in several respects by deprivation alone and by the administration of Dexedrine despite the fact that the last dose was administered 15 hours before bedtime. Examination of the data from baseline sleep and the two recovery nights immediately following 64 hours of deprivation (after Dexedrine and placebo) revealed a number of effects. There were several differences between the baseline night and the recovery nights regardless of whether subjects received Dexedrine or placebo during sustained wakefulness. Generally speaking, sleep onset was faster and the sleep quality was better (higher sleep efficiency and less stage 1 sleep) after the deprivation periods (both with Dexedrine and placebo) than on the baseline night. These results were not surprising in light of the fact that there was significant sleep pressure following 64 hours of continuous wakefulness. Other investigators have reported deprivation-related changes in recovery sleep architecture which have included decreased stage 1 sleep and reductions in the amount of time awake after sleep onset (Bonnet, 1994). In addition to these changes, there also were differences in the quality of recovery sleep related to the administration of Dexedrine versus placebo. In the Dexedrine condition, subjects had received 30 mg of drug on the first deprivation day, and before the total dosage was eliminated (Dexedrine has an average half-life of 10.25 hours), the next series of doses began. Thus, by bedtime on the second

deprivation day, there was probably 10-15 mg of Dexedrine remaining in the participants' systems. This produced some indications of lighter sleep (more stage 1 and less sleep efficiency) as well as disturbed REM sleep after Dexedrine in comparison to placebo. It took longer for subjects to enter REM sleep and they spent less time in REM sleep after Dexedrine than placebo. In addition, four of the six volunteers missed their first REM period after Dexedrine was administered. Many of these findings are consistent with earlier reports of the effects of Dexedrine on sleep architecture following 40 hours of sustained wakefulness in a similar testing situation (Caldwell and Caldwell, 1997).

It is difficult to estimate the impact of altered REM sleep during recovery, especially since the function of REM sleep is not fully understood (Lubin et al., 1974; Johnson et al., 1974). If in fact, REM sleep serves to consolidate memory and/or restore mental resources following wakefulness, it could be that extended use of Dexedrine (in a series of on-again/off-again episodes of sustained operations) might lead to a progressive deterioration in higher-level thought processes. However, it seems unlikely that this would manifest itself very rapidly as long as 1 night of recovery sleep is allowed after 40-hour periods of continuous wakefulness (Caldwell and Caldwell, 1997), and 2 nights of recovery sleep are permitted after 64-hour periods. All of the subjects used in this investigation apparently recovered sufficiently after 2 nights of sleep as evidenced by the lack of condition-by-order effects on a majority of the performance, mood, and EEG data. Also, it should be noted that, while there were statistically-significant differences in sleep architecture following Dexedrine versus placebo, subjects did not spontaneously complain of disrupted sleep after Dexedrine, and no differences were found between Dexedrine and placebo in terms of sleep onset or total sleep time. In addition, there was evidence that stage 3 sleep actually increased after Dexedrine relative to placebo.

Subjective observations

Despite the fact that this study was conducted in a double-blind fashion, it was apparent when the subjects were administered Dexedrine versus placebo. Sometimes it required waiting until the 0500-1100 tests in the deprivation cycle to be relatively certain, but during these times the subject's behavior offered a number of salient cues. Subjects who were under the influence of placebo typically became withdrawn and sluggish; and during the simulator flights, their eyelid closures were noticeably longer. Especially while flying the instrument maneuvers (in which the simulator's windscreen presented an opaque, grey sceen), the subjects obviously had to make heroic efforts to resist falling asleep at the controls. In fact, had it not been for the intervention of the simulator console operator (either engaging the subject in conversation or giving instructions to transition from one maneuver to the next), most volunteers probably would have slept through the middle portion of many of their flights under placebo. Participants often went to sleep for brief periods (less than 1 minute) during the resting EEGs (immediately after the flights) because of the lack of stimulation offered by the dimly lit, sound-attenuated testing booth. Even those who managed to keep their eyes opened during the eyes-open portion of the EEG session, often suffered from lapses in attention and situational awareness.

By the second day of deprivation, participants in the placebo condition had obvious difficulty remembering the parameters of their flight maneuvers despite the fact that they had flown the

same profile at least 8 to10 times at that point. In addition, some of the volunteers under placebo became irritable to the extent that staff members were somewhat reluctant to pressure them to meet the tight daily schedule and perform the next test (although we did it anyway). Fortunately, there were enough personnel conducting the study to boost the subject's interest by rotating in new staff members at key times of the deprivation cycle. Also, the schedule was busy enough to minimize boredom. However, had the volunteers not had access to action-adventure films, games, and occasional opportunities to take walks around the Laboratory, it would have been nearly impossible for some to remain awake during the entire deprivation cycle under the placebo condition (especially during the last 24 hours). It was interesting to note that, despite the fact that all of the subjects had been clearly instructed (and repeatedly reminded) that they must remain awake throughout the entire deprivation period, while under the placebo condition, many of them failed to initiate activity that would have promoted alertness. In fact, staff members typically found it necessary to very strongly encourage even the most highly motivated volunteers to engage in conversation, watch a movie, play games, or walk around in order to prevent lapses into sleep.

Under Dexedrine, the majority of these problems were significantly attenuated. Many of the subjects appeared "normal" or well-rested while under the influence of the drug, and despite the fact that the last dose was given at 0800, most subjects generally remained alert well into the evening of both deprivation days. In fact, about half of the subjects expressed concern that they would not be able to initiate sleep at the conclusion of their deprivation period, but this turned out to be unwarranted since once the lights were turned out, sleep onset occurred rapidly. Several of the staff members who had not previously participated in other Dexedrine studies were amazed at the alertness levels of participants while under Dexedrine in comparison to how these same volunteers appeared under placebo. It was the general consensus of the staff that subjects could have endured a longer deprivation period if Dexedrine had been continuously administered.

Dexedrine administration, however, did produce at least one side effect worthy of mention. Practically all of the subjects in this study (and in some previous studies) became noticeably more talkative under Dexedrine compared to placebo, but two of the volunteers became so talkative that staff members were thankful when the end of their work shifts arrived. One subject in particular appeared to become euphoric under the influence of the drug, and as a result, he talked nonstop throughout his first deprivation day and most of his second, especially during the simulator flights. This behavior raised a concern because this level of excitability had not been observed in any of the other 27 volunteers tested at this Laboratory. As a result, the simulator console operator (who is an experienced standardization instructor pilot with several years of operational experience) was asked to provide a subjective assessment of this volunteer. Specifically he was asked whether or not he felt the volunteer was being adversely affected by Dexedrine to the point of becoming dangerous or careless in the cockpit. In addition, the console operator was asked if he would rather fly with this volunteer while the volunteer was on placebo or while he was on Dexedrine. In answer to the first question, the console operator indicated that although the research subject was talkative to the point that he would irritate other crew members in the actual flight environment, his flight performance was not reckless or in any way dangerous other than the fact that he might miss some detail because of his involvement in conversation. In

answer to the second question, the console operator indicated that there was no doubt that he would rather fly with this volunteer under the influence of Dexedrine as opposed to placebo because at least the subject was alert under Dexedrine rather than falling asleep on the controls (as was the case under placebo). This last comment would apply to all of the other participants as well.

In addition to the unexpected reaction from one volunteer under Dexedrine and the other problems (principally under placebo) associated with sleepiness and fatigue throughout the entire sample, there were a couple of other minor difficulties as well. A couple of volunteers reported slight vestibular disturbances which appeared to be related to the prolonged period of sleep deprivation. In one case, these disturbances disappeared under Dexedrine versus placebo, but in the other, they remained under both conditions. Other participants occasionally complained of indigestion or headache, but none of these were severe enough to warrant treatment other than with acetominophen or ibuprophen. Some volunteers complained of eye irritation which was alleviated with saline eye drops. About half of the volunteers also commented that they could feel their heart beats while under the influence of Dexedrine, but this apparently did not cause them undue concern or interfere with their performance (one subject did experience a disconcerting increase in diastolic blood pressure--slightly above 100 mmHg--, but retaking the pressure in a prone position maintained it within protocol limits). Otherwise, there were no noteworthy side effects.

Summary and conclusions

In summary, this study indicated that prophylactic administration of Dexedrine sustained flight performance, physiological arousal, and mood throughout 64 hours of continuous wakefulness, whereas placebo did not. Administering three 10-mg doses (at midnight, 0400, and 0800) on each of the two deprivation days substantially reduced the impact of sleep loss in the early morning hours and, for the most part, preserved performance for the remainder of the day. The beneficial effects of Dexedrine were most readily apparent during the circadian trough which extended from approximately 0300 until 1200 on both days (the low point in body temperature was at about 0800). At these times, performance and alertness under placebo were most significantly impaired. There were no clinically-significant side effects attributable to Dexedrine which caused the discontinuation of any participant; however, one subject experienced an increase in diastolic blood pressure that would have been cause for concern had it not decreased when the subject was retested in a prone position. Some of the aviators complained of palpitations and "jitteriness" under Dexedrine, but this did not detract from their performance. One of the subjects became very excitable and talkative under the influence of Dexedrine, but his flight performance remained stable and was substantially better than it was under placebo.

Analysis of the recovery sleep periods suggested that a minimum of two 8-hour nights of recovery sleep should be required for anyone who is administered sufficient Dexedrine to remain awake continuously for 64 hours. Dexedrine does reduce the restorative nature of recovery sleep because of its long half-life of 10.25 hours (Physicians Desk Reference, 1998); however, the

results of this study suggest that performance and alertness were restored by two nights of uninterrupted sleep.

Thus, Dexedrine should be considered an appropriate countermeasure for sleep loss in operational environments where short-term (i.e., 64 hours) sleep deprivation is unavoidable. Although there is no substitute for adequate sleep, Dexedrine's positive effects on alertness could make the difference between life and death in prolonged periods of continuous wakefulness, especially in the morning hours when the drive for sleep becomes overpowering.

Prior to using Dexedrine in the operational context, personnel should be exposed to a test-dose regime under controlled conditions. It may be necessary to make individualized adjustments to dosages or dose schedules in some cases, although this appears unlikely based on the data from the present sample of 6 aviators (or any of the 22 aviators tested previously).

Whether Dexedrine administration would continue to preserve performance in periods of sleep deprivation longer than 64 hours remains unclear at present. In order to fully answer this question, a follow-on study should be conducted in which the drug is used to maintain the alertness and performance of aviators for up to 112 hours. This is being planned for the future.

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Appendix A.

Flight maneuvers.**

Maneuver	Description
1. Low hover	Maintain hdg 150°, alt 10 ft
2. Low hover turn	Hdg from 150° to 330° while holding alt of 10 ft above ground
3. High hover	Maintain hdg 330°, alt 40 ft
4. High hover turn	Hdg from 330° to 150°, holding alt of 40 ft above ground level
5. Navigate to chkpt 1	Maintain GPS hdg, 700 feet MSL, arrive at checkpoint in 3 min
6. Navigate to chkpt 2	Maintain GPS hdg, 600 feet MSL, arrive at checkpoint in 2 min
7. Navigate to chkpt 3	Maintain GPS hdg, 600 feet MSL, arrive at checkpoint in 5 min
8. Navigate to chkpt 4	Maintain GPS hdg, 600 feet MSL, arrive at checkpoint in 2 min
9. Navigate to chkpt 5	Maintain GPS hdg, 700 feet MSL, arrive at checkpoint in 4 min
10. Transition	Establish hdg 360°, airspeed 120 k and alt 2000 ft MSL
11. Straight & level	Maintain the above parameters 1 min
12. Left Std Rt Turn	Perform 360° left turn maintaining airspeed and alt
13. Straight & level	Maintain hdg 360°, airspeed 120 k and alt 2000 ft for 1 min
14. Climb	Climb from 2000 to 2500 feet maintaining hdg and airspeed
15. Right Std Rt Turn	Perform 180° right turn maintaining airspeed and alt
16. Straight & level	Maintain hdg 180°, airspeed 120 k, and alt 2500 ft for 1 min
17. Right Std Rt Turn	Perform 180° right turn maintaining airspeed and alt
18. Climb	Climb from 2500 to 3500 feet maintaining hdg and airspeed
19. TURN AFCS OFF	----------
20. Descend	Descend from 3500 to 3000 feet maintaining hdg and airspeed
21. Left Des Std Rt Turn	Turn left 180° , while descending 500 ft maintaining airspeed
22. Descend	Descend from 2500 to 2000 feet maintaining hdg and airspeed
23. Left Std Rt Turn	Perform 180° left turn maintaining alt and airspeed
24. Straight & level	Maintain hdg 360°, airspeed 120 k,alt 2000 ft for 2 min
25. Right Std Rt Turn	Perform 360° right turn while maintaining alt and airspeed
26. Descend	Descend from 2000 to 1000 feet maintaining hdg and airspeed
27. TURN AFCS ON	------MOVE TO COORDINATES------
28. Execute terrain flt approach to LZ	Maintain airspeed until approach angle intercept, touch down in Y
29. Formation departure (stagger left)	Maintain 3 rotor disk separation at 30° angle depart simultaneously with lead ship
30. Formation flight w lead	Maintain 3 rotor disk separation at 30° angle (stagger left)
31. Formation flight w lead (trail)	Maintain 3 rotor disk separation behind (trail)
32. Perform formation approach w lead	Maintain 3 rotor disk separation behind (trail), touch down simultaneously with lead ship

** Only the upper-airwork maneuvers, numbers 11-26, are discussed in this report.

Appendix B.

Manufacturer's list.

Advanced Gravis Computer Tech., Ltd.
1790 Midway Lane
Bellingham, WA 98226

Altec Lansing Technologies, Inc.
Milford, PA 18337

Cadwell Laboratories
909 North Kellogg Street
Kennewick, WA 99336

C. H. Products
970 Park Center Drive
Vista, CA 92083

Coulbourn Instruments, Inc.
Box 2551
Lehigh Valley, PA 18001

Creative Labs, Inc.
1901 McCarthy Blvd.
Milpitas, CA 95035

Digital Equipment Corp.
P.O. Box C52008
Nashua, NH 03061-2008

Elexor Associates
P.O. Box 246
Morris Plains, NJ 07950

Grass Instrument Co.
101 Old Colony Ave.
Quincy, MA 02169

IVAC Corp.
10300 Campus Point Dr.
San Diego, CA 92121

MicroSoft
1 Microsoft Way
Redmond, WA 98052

Nihon Kohden
17112 Armstrong Ave.
Irvine, CA 92714

SensorMedics
22705 Savi Ranch Parkway
Yorba Linda, CA 92678