



**An In-Flight Investigation of the Efficacy of  
Dextroamphetamine for the Sustainment  
of Helicopter Pilot Performance**

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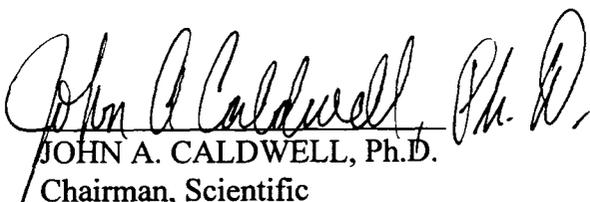


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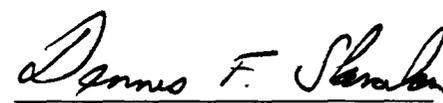
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1 hour prior to each of the first three sessions (for a total of 30 mgs). During the other period, the subjects were administered placebos. A double-blind administration scheme was used, and drug orders were counterbalanced. Vital signs were monitored at regular intervals throughout the study.

Results indicated significantly smaller flight control errors under Dexedrine versus placebo on at least one measure in four of the seven maneuvers, and tendencies ( $p=10$ ) toward smaller errors under Dexedrine versus placebo on two of the three remaining maneuvers. Dexedrine was especially helpful during the morning hours when the combined impact of circadian factors and fatigue most severely degraded alertness. Differences between Dexedrine and placebo tended to be accentuated in maneuvers flown without the aid of the UH-60's automatic flight-path stabilization system. Of the 19 drug-related flight performance effects found in this investigation, only 2 were in the opposite direction of what was expected.

Dexedrine also sustained other aspects of performance better than placebo on some, but not all, of the non-flight tests. Although Dexedrine administration had little effect on performance of the desktop flight simulator or the simulated fuel management part of the Multi-Attribute Task Battery (MATB), there were several Dexedrine-related improvements on other parts of the MATB including systems monitoring, communications, and tracking. Subjective mood ratings of depression, fatigue, and confusion were lower under Dexedrine in comparison to placebo. Conversely, feelings of vigor and activity were higher under Dexedrine. Several of the performance and mood changes showed Dexedrine was especially helpful in the mornings. Central nervous system arousal also was elevated by Dexedrine. Critical fusion frequency was higher (during descending trials only), slow-wave EEG power (theta) was lower, and faster EEG alpha activity was more prominent under Dexedrine than placebo. Subjects clearly were better able to stay awake after drug administration.

Sleep quality was degraded the night following Dexedrine, despite the fact that the last dose was given 15 hours prior to bedtime. Although the deepest stages of sleep were unaffected, the amount of REM sleep was reduced, REM latency was increased, and the percentages of stages 1 and 2 sleep were greater on the night after Dexedrine than after placebo. These changes probably are not operationally significant where Dexedrine will be used occasionally, but after repeated administrations, the cumulative sleep debt will ultimately impair alertness and performance.

In summary, it appears the results of this in-flight investigation support the conclusions of earlier simulator studies performed at this Laboratory. Dexedrine appears to be a safe and effective countermeasure for the short-term sustainment of aviator performance in sustained operations. However, the advisability of using Dexedrine for longer periods (i.e., more than 40 hours of continuous wakefulness) remains to be determined in future research.

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## Introduction

The primary purpose of this investigation was to establish the efficacy of Dexedrine for sustaining actual in-flight aviator performance despite moderate amounts of sleep loss. Although earlier laboratory studies of Dexedrine yielded favorable results with no significant side effects, it is important to verify these findings in the actual flight environment before making final operational recommendations. The reason for this is that there are simulator/in-flight differences in motivational factors (more fear of crashing in the aircraft) and environmental factors (more noise, vibration, and turbulence in the aircraft) which will likely affect flight performance. It is possible that the differences between Dexedrine's effects in the two situations (simulator versus in-flight) either could be potentiated or moderated. At present, the effects of this medication on actual in-flight performance are unknown.

To explore the in-flight effects of Dexedrine, computerized evaluations of aviator flight skills were conducted by the U.S. Army Aeromedical Research Laboratory (USAARL) at regular intervals as subjects completed standardized flights in a UH-60 helicopter. Laboratory-based assessments of cognitive, psychological, and central nervous system status were conducted as well to determine the effects of Dexedrine on general levels of alertness. This investigation follows recently completed UH-60 simulator studies, and the outcomes were of interest in terms of verifying the efficacy of Dexedrine in the in-flight environment.

## Military relevance

Current military doctrine requires that Army aviation units operate around the clock during times of conflict because the success of battlefield operations depends on maintaining the momentum of continuous day-night operations (Department of the Army, 1989). In part, due to the significant improvement in night fighting capability offered by night vision goggles, 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 round-the-clock operations. Although aircraft can function for extended periods without adverse effects, human operators need periodic sleep for the restitution of both the body and the brain (Horne, 1978). Depriving humans of proper restorative sleep produces attentional lapses and slower reaction times which are associated with poor performance (Krueger, 1991).

Because it is virtually impossible for aviation crews to receive adequate sleep and rest during combat operations, it is essential that the military explore countermeasures to offset the performance decrements associated sleep debt. Given that personnel resources are dwindling while mission demands are expanding, pharmacological countermeasures (i.e., stimulants) may be the only viable alternative in some situations.

## Background

### General

A variety of different strategies have been investigated to minimize fatigue-related performance decrements in various work settings (Babkoff and Krueger, 1992), but the combat situation remains problematic because it is intense and unpredictable. As Cornum (1994) has pointed out, while it is desirable to control the timing and duration of sleep periods via sleep management programs, this approach often is not feasible in the operational setting. One illustration of this fact was offered by recent research which suggested that despite commanders' best efforts to properly manage crew rest in the combat environment, sleep deprivation was a problem for Army pilots during Desert Storm even though the combat period was short (Caldwell, 1992). In addition, it has been reported that Air Force F-15C pilots suffered significant fatigue and circadian disruptions when flying combat air patrol missions over Iraq (Cornum, 1994).

When operational constraints prevent the use of behavioral strategies for the alleviation of aircrew fatigue, pharmacological countermeasures (stimulants) may be the only option for maintaining aviator performance. Of the pharmacological compounds available, it has been suggested that amphetamines offer the greatest potential for counteracting performance decrements attributable to sustained operations (Shappell, Neri, and DeJohn, 1992). Since dextroamphetamine is the most potent of the amphetamines (Smith and Davis, 1977), Dexedrine has been the stimulant of choice in several studies and in the operational environment.

### Dexedrine

Dexedrine (SmithKline Beecham) is dextroamphetamine sulfate, supplied in 5, 10, and 15 mg Spansule sustained-release capsules, 5 mg tablets, and an elixir supplying 5 mg amphetamine per 5 ml (Physicians' Desk Reference, 1993). Dexedrine is a sympathomimetic amine.

Although the sympathomimetic amines differ somewhat in their effects based on differing amounts and types of central and peripheral stimulation (Benowitz, 1990), they have broad actions which can be classified as: 1) peripheral excitatory (stimulates certain smooth muscles like those in blood vessels of the skin, mucous membranes, and glands like salivary and sweat glands); 2) peripheral inhibitory on other smooth muscles (like those in the gut, blood vessels supplying skeletal muscles, and the bronchial tree); 3) cardiac excitatory (increased heart rate); 4) metabolic actions (increased glycogen conversion in liver and muscle); 5) endocrine actions (modulation of insulin and pituitary hormones); and 6) central nervous system (CNS) effects (increased wakefulness and motor activity with reduced appetite) (Weiner, 1980). As discussed below, dextroamphetamine has many, but not all of these effects.

Generally, the actions of amphetamines are similar to those of epinephrine. Dextroamphetamine exerts its effects by enhancing the release of norepinephrine and dopamine (Carlson, 1977).

### Typical effects

Dextroamphetamine has both CNS and peripheral effects (Weiner, 1980). Oral amphetamine elevates blood pressure (systolic and diastolic), but does not increase heart rate or cerebral blood flow. The bronchial muscle is slightly relaxed, but respiration rate and volume are unaffected. The urinary bladder sphincter is constricted. Gastrointestinal effects are not predictable. The CNS is stimulated, particularly with d-amphetamine, and the depressant effects of other drugs are lessened. Psychological effects of doses ranging from 10-30 mg are increased wakefulness, alertness, initiative, and concentration, with elevated mood, sometimes euphoria, improved task performance, and decreased fatigue. Amphetamines have been used to prolong performance of vigilance tasks, and in situations where performance has degraded due to sleep loss, amphetamines have produced improvements in tasks requiring sustained attention. Amphetamines alter sleep electroencephalographic (EEG) activity by cutting in half the typical amount of REM sleep. They alter the waking EEG by increasing desynchronous activity and producing a shift toward higher frequencies. Amphetamine suppresses the appetite probably via the lateral hypothalamus. Occasionally, amphetamine will produce a slight elevation in body temperature.

### Dosage

The usual chronic oral dose of dextroamphetamine is 5 mg, 2-3 times daily; however, studies employing the drug to prolong wakefulness typically employ larger doses in the range of 10-20 mg (Weiss and Laties, 1967). Prior to administering normal therapeutic doses to humans, a test dose of 2.5 mg is recommended since toxic manifestations have been seen (as an idiosyncrasy) after even a 2 mg dose, although reactions are rare with doses under 15 mg.

### Pharmacokinetics

A single dose of two 5-mg tablets has been shown to produce an average peak blood level of 29.2 ng/ml at approximately 2 hours. The average half life is 10.25 hours (Physicians' Desk Reference, 1993).

### Adverse reactions

The most common cardiovascular adverse effects are palpitations, tachycardia, and elevated blood pressure. The most common adverse CNS reactions are overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, tremor, and headache. The most common adverse gastrointestinal reactions are dryness of mouth, diarrhea, or constipation (Physicians' Desk Reference, 1993).

## Tolerance and toxicity

Although the amphetamines can be toxic at doses only slightly higher than the recommended dose, tolerance develops quickly with repeated use. Thus, it will be necessary to increase dose amounts to achieve a consistent therapeutic effect with chronic administration. Ingestion of an acute dose of 1 mg/kg is considered life-threatening (Benowitz, 1990). In the event of acute intoxication, chlorpromazine and an alpha-receptor blocking agent should reduce both the CNS and the pressor effects of amphetamine (Weiner, 1980); however, Benowitz (1990) reports that there is no specific antidote. He recommends: 1) maintaining airways and assisting ventilation; 2) treating symptoms of agitation, seizures, coma, and hyperthermia; 3) monitoring vital signs and electrocardiogram (EKG) for at least 6 hours; 4) treating hypertension, tachyarrhythmias, and arterial vasospasm; and 5) performing gastric lavage and administering charcoal and a cathartic.

### Aviation performance studies

Numerous investigations have proven that amphetamines are effective for enhancing physical performance, vigilance, alertness, cognition, and military performance (see Caldwell et al., 1994 for a review), but there have been very few aviation-related studies. However, the few studies which exist support the contention that amphetamines are effective countermeasures for sleep loss and fatigue in aviation personnel.

Pascoe, Nicholson, and Turner (1994) suggested that sometimes, even in situations where they do receive enough sleep, aviators may require pharmacological assistance to maintain appropriate levels of alertness required in fatiguing continuous combat operations.

Senechal (1988) reported that EF-111A Raven jet crews who were administered 5 mg Dexedrine during an Air Force strike on Libya in April of 1986 experienced positive effects in terms of overcoming the fatigue of the mission itself and the sleep deprivation which occurred during earlier preparation for the mission. There were no in-flight or landing problems, and all of these electronic-jamming aircraft returned safely to base.

Cornum (1992) reported that dextroamphetamine also was used with 35 F-15C pilots who were flying combat air patrol missions during Operation Desert Shield/Storm. These pilots were not only flying long missions (6-11 hours), but were sleep deprived and suffering from circadian desynchronization as well. To counteract potentially lethal performance decrements, the pilots were issued five to six dextroamphetamine tablets (5 mg) at the beginning of flights and were told to self-administer one tablet every 2-4 hours as needed to maintain alertness until landing. The aviators reported clear benefit from the drug, and the unit commander ultimately concluded that dextroamphetamine administration contributed significantly to the safety of 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.

Emonson and Vanderbeek (1993) indicated that Air Force pilots effectively used dextroamphetamine during Operation Desert Storm to maintain acceptable performance during continuous and sustained missions. The medication was found to be both safe and beneficial in terms of overcoming fatigue without producing unwanted side effects.

These anecdotal reports recently have been supported in a controlled laboratory investigation of the effects of Dexedrine on sleep deprived aviators. Caldwell, Caldwell, and Crowley (1996) conducted placebo-controlled studies of 12 Army helicopter pilots who completed UH-60 simulator flights, psychological evaluations, and electrophysiological assessments throughout 36-hour sleep deprivation periods. Simulator flights occurred at 0100, 0500, 0900, 1300, and 1700. One hour prior to each of the first three flights, the aviators were given 10 mg of Dexedrine or placebo. Analyses of the flight maneuvers revealed that Dexedrine improved aviator control on the majority of maneuvers including the descents, straight-and-levels, standard-rate turns, stationary hovers, low-level navigation, and a left-descending turn. Performance was not enhanced on hovering turns or formation flight. The times of day at which Dexedrine most noticeably facilitated flight performance were 0500, 0900, and 1700 (after 22, 26, and 34 hours of continuous wakefulness). EEG and mood data showed that general alertness also was sustained significantly by Dexedrine. Although the quality of recovery sleep after Dexedrine was somewhat compromised, there were no clinically significant behavioral or physiological effects in any of the subjects. Thus, it appears that Dexedrine is a safe and effective means for sustaining helicopter pilot performance during short periods of sleep loss. However, this should be verified in the actual flight environment before Army policy relevant to the administration of stimulants to aviators is updated.

### Objectives

This investigation was designed to determine the effects of dextroamphetamine (Dexedrine) in safely sustaining alertness and performance of helicopter pilots despite sleep loss in an aviation context. The study employed a variety of assessments to determine the effects of repeated 10-mg doses of Dexedrine on: *flight performance* measured in a UH-60 helicopter, *CNS function* measured by EEG, *psychomotor & cognitive skill* measured by a desktop simulator, *mood* measured by the Profile of Mood States (POMS), *cortical activation* measured partially by critical flicker fusion, *vigilance and cognition* measured by the Multi-Attribute Task Battery (MATB), *sleep architecture* measured by polysomnography.

In addition, this investigation evaluated the comparability between flight performance assessments made in the UH-60 simulator (from a previous study) to those made in a UH-60 aircraft during actual in-flight conditions.

## Methods

### Subjects

Ten UH-60 qualified and current aviators were recruited to reside in the USAARL test facility for a period of 1 week each. Aviators were individually tested on the designated tasks while remaining in Laboratory the entire time (except during flights). The mean age of these volunteers was 31.9 years (ranging from 28 to 36), mean weight was 186.9 pounds (ranging from 155 to 235), and mean total hours of past flight experience was 1277.9 hours, with an average of 839 hours in the UH-60 (ranging from 85 to 2200 hours). Efforts were made to test both male and female subjects; however, only males volunteered for the study (about 97.5 percent of Army aviators are male). Gender should not be a concern based upon the results of two earlier simulator studies and an examination of the existing literature--gender differences in terms of responsiveness to Dexedrine or sleep deprivation have not been observed (Caldwell, Caldwell, and Crowley, 1996).

The subjects participating in this research all had current military flight physicals. The subjects were examined by a USAARL flight surgeon. The examination included a review of the standard medical history and flight medical history, and a physical examination to include an EKG. Subjects would have been excluded if there had been evidence of a current illness, significant arteriosclerosis, cardiovascular disease, hypertension, hyperthyroidism, hypersensitivity to sympathomimetic amines, glaucoma, prostate or bladder disorders, neurological conditions including migraine disorder, drug abuse, recent use of monoamine oxidase inhibitors, psychological agitation, psychiatric disturbances, or sleep disturbances; however, none of the potential subjects had any of these problems.

Prior to the study, all test subjects were thoroughly briefed on the nature, duration, and purpose of the research. The methods and means by which it was to be conducted, the inconveniences and hazards associated with the project, and the precautions and safety measures that could have been required during the experiment were explained. All participants in this investigation were fully briefed concerning their right to withdraw from participation at any time without penalty and gave their informed consent based on institutional review committee requirements.

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. Tobacco users were not excluded from this protocol, and 5 of the 10 subjects used some form of tobacco (1 used cigarettes, 4 used smokeless) on a regular basis prior to the study and during the study (although in-study use of tobacco was restricted to the time period surrounding the flights and prohibited in between tests during sessions).

## Apparatus

### Physiological data

Oral temperatures were collected with an IVAC thermometer\* (Model number 811). Pulse and blood pressure data were collected either with a Critikon vital signs monitor\* (Model number 1846SX) or a conventional sphygmomanometer. An initial EKG was taken with a Marquette Microcomputer Augmented Cardiograph system\*.

### UH-60 aircraft

All flights were conducted in USAARL's specially instrumented UH-60 helicopter equipped with a computerized flight monitoring system referred to as the Aeromedical Instrumentation System (AIS). This system was used to monitor pilot performance during each flight and to record these data for later analysis. The AIS consists of an interconnect wiring harness, a 32-channel signal conditioner, and a computerized recording system. The wiring harness, which is permanently installed in the aircraft, interconnects the aircraft's flight control system, pitot-static system, navigational system, and other electronic systems to a signal conditioner located in a removable rack in the rear cabin area. Signals output from the conditioner are converted to digital form by a data acquisition unit, and these data are stored in real time in the memory of a Paravant RHC-88 ruggedized hand-held computer\*.

The wiring harness and signal conditioning equipment were designed, fabricated, and installed by USAARL personnel. The data acquisition unit is a commercially available Elexor PL-1000\*. This unit converts the conditioned analog signals to digital form and outputs them as ASCII data to the hand-held computer through an RS-232 serial link. These components permit the continuous monitoring of the aircraft parameters listed in table 1.

At the conclusion of each flight, the RHC-88 computer was brought back to the Laboratory for "downloading" to a computer. The flight data was then converted to a format suitable for further analysis on the VAX.\* Data transfer to the VAX was accomplished on the local area network.

### EEG evaluations

The EEG evaluations conducted during each subjects' waking periods were performed with a Cadwell Spectrum 32 neurometric analyzer.\* This device permitted the collection of seven channels of EEG data (Fz, C3, Cz, C4, Pz, O1, O2) which were stored on optical disks for subsequent analysis. For the collection of resting EEG, the low filter was set at 0.53 Hz, the high

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\*See manufacturers' list.

Table 1.  
Flight parameters measured by the AIS.

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<u>Parameter</u>	<u>Range</u>	<u>Units</u>
1. Barometric altitude	0-10,000	feet
2. Indicated airspeed	30-180	knots
3. IVSI	0 +/- 3,000	feet per minute
4. Magnetic heading	0-360	degrees
5. Pitch angle	0 +/- 30	degrees
6. Roll angle	0 +/- 60	degrees
7. Radar altitude	0-1500	feet
8. Torques (engine #1 & #2)	0-110	percent
9. Cyclic fore-aft position	0 +/- 100	percent
10. Cyclic left-right position	0 +/- 100	percent
11. Collective position	0 +/- 100	percent
12. Pedal position	0 +/- 100	percent
13. Slip	0 +/- 2	ball widths
14. Localizer/course dev.	0 +/- 2	dots
15. Glide slope deviation	0 +/- 2	dots
16. Stabilator position	-10 to +40	degrees
17. Turn rate	0 +/- 1	standard rate turn
18. GPS navigation data	Position/groundspeed	degrees/knots
19. AFCS <sup>1</sup> trim positions	0 +/- 100	percent
20. Master caution light	On/off	n.a.
21. Pedal switch position	Open/closed	n.a.
22. Trim release button pos.	Open/closed	n.a.

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Note: Only a subset of these were used in the present study as is noted in the Results section of this report. Measured parameters changed depending upon the maneuver being conducted.

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<sup>1</sup> The automatic flight control system (AFCS) improves the stability and handling qualities of the UH-60. Normally, the AFCS is engaged when flying this aircraft.

filter was set at 70 Hz, and the 60 Hz notch filter was used. For the collection of P300s, the high filter was increased from 70 to 100 Hz. The stimuli which were used for the visual P300 (evoked potential) were presented on a 15-inch monitor located approximately 1 meter from the subject. For the auditory P300, stimuli were presented binaurally via Etymotic earphones. All test sessions were conducted in a dimly-illuminated, sound-attenuated chamber.

### Desktop flight simulation task

The desktop flight simulation task consisted of the Microsoft Flight Simulator 4.0<sup>®</sup>,\* combined with a custom-designed, timed flight course (Microsoft Aircraft and Scenery Designer<sup>®\*</sup>). This task was run on a 486 computer with VGA graphics. Flight control was via a Virtual Pilot flight yoke (CH Products<sup>®</sup>),\* with system interface using either mouse or keyboard. An auditory distractor task in which the subject was required to press a button upon the delivery of a low-pitched tone was performed concurrently with each flight. Tone presentations and reaction time recordings were made with Coulbourn Instruments equipment.\*

### Mood questionnaire

The subjective evaluations of changes in mood were made with the POMS (McNair, Lorr, and Droppelman, 1981). The POMS is a 65-item paper and pencil test which measures affect or mood on 6 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.

### Critical fusion frequency

Changes in a behavioral indicator of cortical activation were evaluated with a Lafayette model 12023 critical fusion frequency (CFF) threshold testing unit.\* This unit consists of a flicker control unit which automatically varies the flicker rate of a light source presented to both of the subject's eyes. A hand-held pushbutton is used by the subject to indicate CFF threshold, which is displayed on an liquid crystal display (LCD) panel.

### Cognitive tests

Changes in aviation-related cognitive and psychomotor abilities were examined with the MATB. This test required that subjects 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 periodically required to change "radio frequencies." It was administered via a 386 computer with a standard keyboard, a joystick, and a 13-inch color monitor.

## Polysomnography

Evaluations of whether subjects experienced sleep disturbances as a function of drug were made during subjects' recovery sleep periods using a Nihon Kohden electroencephalograph (model No. EEG-4321P).<sup>\*</sup> The EEG data were collected using a subset of the same electrodes attached for the recording of the waking EEG (C3, C4, O1, O2, A1, and A2). Four additional electrodes (SensorMedics),<sup>\*</sup> 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 60 Hz notch filter was not employed.

### Procedure

Test sessions were conducted at 0900, 1300, and 1700 on Monday, Tuesday, and Thursday; and at 0100, 0500, 0900, 1300, and 1700 on Wednesday and Friday (the sleep deprivation periods). On Wednesday and Friday, drug or placebo doses were administered to subjects at 0000, 0400, and 0800 (1 hour prior to each of the first three sessions), as can be seen in table 2. At each dose time, subjects received two orange capsules containing either 5 mg Dexedrine each (for a total of 10 mg per two-capsule dose), or lactose placebo administered with 8 ounces of orange juice.

Each test session began with a flight in the UH-60 and ended with administration of the MATB. Approximately 30 minutes prior to each flight, the subject was transported to Cairns Army Airfield where he met the safety pilot. The safety pilot already had preflighted the aircraft by the time of the subject's arrival. Once the subject, the safety pilot, and the AIS operator were situated in the aircraft, preflight checklists were completed, and the aircraft run-up was done; and once departure clearance was obtained, the flight began. Attempts were made to depart as closely as possible on the hour; however, traffic and weather delays often made this impossible. At the conclusion of each flight, the subject was transported back to USAARL to complete the other tests.

### Flight performance testing

The flight evaluations required subjects to perform a variety of precision maneuvers of the type typically flown in a UH-60 (see table 3). This flight profile consisted of upper-airwork in which the subjects flew precision maneuvers based upon instrument information. All flights were flown unaided (no night vision goggles). The flight profile was designed to allow flights under instrument meteorological conditions (IMC), to reduce the impact of adverse weather; however, due to safety factors, normal instrument flight rule (IFR) minimums were replaced with more conservative minimums of 1000-foot ceilings and 3 miles of visibility. The same sequence

of maneuvers was used for every subject during each of the flights. These maneuvers are fully described in the Aircrew Training Manual (Department of the Army, 1988).

There were a total of 15 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, two standard-rate descents, one left descending turn, and an instrument landing system (ILS) approach into Cairns Army Airfield. During each of the upper airwork maneuvers, 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 ideal flight parameters during each maneuver.

The computer calculated root mean square (RMS) errors for a variety of measures within each of the flight maneuvers in order to express how well subjects maintained specific headings, altitudes, airspeeds, and other parameters. These data were subjected to log natural transforms prior to analysis in order to minimize the impact of extreme scores. The entire flight usually lasted from 30-60 minutes, depending on weather and traffic. The flight profile was performed in the USAARL flight testing area, and the maneuvers began at a time similar to the times at which these maneuvers were conducted in earlier simulator studies. A safety pilot (non-sleep deprived), was in command of each flight from the left front seat of the aircraft. He supervised all aspects of the flight and ensured the correct timing and sequencing of each maneuver. An AIS operator in the rear of the aircraft operated the computerized monitoring system.

### EEG evaluations

Each EEG session lasted approximately 30 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 sit quietly with eyes opened for 1.5 minutes followed by 1.5 minutes of eyes closed while data are recorded. After the resting EEG, subjects were given a visual P300 (evoked potential) task during which they counted the number of rare stimuli presented among common stimuli. The rare stimuli consisted of 64 x 64 check patterns presented on a 15-inch black-and-white monitor. The common stimuli consisted of 4 x 4 check patterns. The stimuli were presented at a rate of 1 stimulus every 0.91 second, and there were 40 rare stimuli presented among 160 common stimuli. After the visual P300, an auditory P300 was conducted. The task consisted of a series of 200 tones presented simultaneously to both ears. The rare stimuli were 70 dB, 2000 Hz tones with a rise time, a plateau, and a fall time of 10 msec, a cosine envelope, and a fixed phase with no masking noise. The common stimuli were identical, with the exception of the frequency, which was 500 Hz. The rare tones were randomly presented 40 times among the 160 common tones at a rate of 1 stimulus every 0.91 second.

Table 2.  
Testing schedule.

TIME	SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
00-01				DEX/PBO		DEX/PBO	
01-02				aircraft		aircraft	
02-03		s l e e p	s l e e p	eeg dsktp sim	s l e e p	eeg dsktp sim	s l e e p
03-04				poms/cff MATB		poms/cff MATB	
04-05				DEX/PBO		DEX/PBO	
05-06				aircraft		aircraft	
06-07				eeg dsktp sim		eeg dsktp sim	
07-08		wake up	wake up	poms/cff MATB	wake up	poms/cff MATB	wake up
08-09		testdose breakfast	breakfast	DEX/PBO breakfast	breakfast	DEX/PBO breakfast	breakfast RELEASE
09-10		aircraft	aircraft	aircraft	aircraft	aircraft	
10-11		eeg dsktp sim	eeg dsktp sim	eeg dsktp sim	eeg dsktp sim	eeg dsktp sim	
11-12		poms/cff MATB	poms/cff MATB	poms/cff MATB	poms/cff MATB	poms/cff MATB	
12-13		lunch	lunch	lunch	lunch	lunch	
13-14		aircraft	aircraft	aircraft	aircraft	aircraft	
14-15		eeg dsktp sim	eeg dsktp sim	eeg dsktp sim	eeg dsktp sim	eeg dsktp sim	
15-16		poms/cff MATB	poms/cff MATB	poms/cff MATB	poms/cff MATB	poms/cff MATB	
16-17							
17-18		aircraft	aircraft	aircraft	aircraft	aircraft	
18-19	arrive	eeg dsktp sim	eeg dsktp sim	eeg dsktp sim	eeg dsktp sim	eeg dsktp sim	
19-20	med exam						
20-21	eeg	poms/cff	poms/cff MATB	poms/cff MATB	poms/cff MATB	poms/cff MATB	
21-22		dinner pt	dinner pt	dinner pt	dinner pt	dinner pt	
22-23	practice	shower poms	shower	shower poms	shower	shower poms	
23-24	bedtime	bedtime	poms	bedtime	poms	bedtime	

Note: DEX = Dexedrine dose (10 mg), PBO = Placebo

Table 3.  
Flight maneuvers.

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<u>Maneuver</u>	<u>Description</u>
Straight & level	Maintain heading 270°, airspeed 120 k, altitude 2000 ft for 1 min
Left standard rate turn	Perform 360° left turn maintaining airspeed and altitude
Straight & level	Maintain heading 270°, airspeed 120 k, altitude 2000 ft for 1 min
Climb	Climb from 2000 to 2500 ft maintaining heading and airspeed
Right standard rate turn	Perform 180° right turn to 090° maintaining airspeed and altitude
Straight & level	Maintain heading 090°, airspeed 120 k, altitude 2500 ft for 1 min
Right standard rate turn	Perform 180° right turn to 270° maintaining airspeed and altitude
Climb	From 2500 to 3500 ft maintaining heading and airspeed
TURN AFCS OFF	-----
Descend	Descend from 3500 to 3000 ft maintaining heading and airspeed
Left descending turn	Perform 180° left turn descending from 3000 to 2500 ft
Descend	Descend from 2500 to 2000 ft maintaining heading and airspeed
Left standard rate turn	Perform 180° left turn maintaining altitude and airspeed
Straight & level	Maintain heading 090°, airspeed 120 k, altitude 2000 ft for 2 min
Right standard rate turn	Perform 360° right turn maintaining altitude and airspeed
TURN AFCS ON	-----
Vectored flight and ILS	Intercept the localizer beacon and perform an instrument approach

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The EEGs for eyes-open and eyes-closed were visually scanned for three relatively artifact-free 2.5-second epochs on which absolute power values were calculated for each of four bands. The results were then averaged together 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). The P300s would have been scored in terms of the amplitudes and latencies of 4 peaks/troughs; however, the fact that subjects found it impossible to remain awake during this task invalidated the results.

### 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. 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. In addition, there was a secondary task which required subjects to discriminate between high- and low-pitched tones presented every 20-seconds while flying the desktop simulator. The subject was required to press a button immediately following the presentation of each low-pitched tone, and reaction times were measured.

### POMS

The POMS was given after each desktop flight simulation test. Subjects were presented with a series of 65 words describing mood states, and for each "mood state" the subject indicated on a standardized answer sheet how well it described the way he was presently feeling. This test took approximately 5 minutes to administer and yielded scores on the factors of tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment.

### CFF

Following the POMS, subjects engaged in a 5-minute test of CFF thresholds. Each test consisted of three ascending trials and three descending trials. In the ascending trials, subjects viewed a light source which flickered at a gradually increasing rate (starting from 0 Hz) and indicated when the light appeared to transition from flickering to continuous. In the descending trials, subjects viewed a light source which flickered at a gradually decreasing rate (starting from 100 Hz) and indicated the point at which the light appeared to transition from continuous to flickering. A pushbutton was used to indicate the transition points in each case. The results of the three ascending trials were averaged together and those of the descending trials were averaged together to produce two CFF scores per session.

### Cognitive performance evaluations

Following the CFF determination, subjects completed a 20-minute session on the MATB. This test required subjects to simultaneously monitor and respond to several tasks which were presented at various locations on the computer screen. The test is an aviation-oriented simulation which presents indications of fuel levels, engine conditions, and pumps which the subject must correctly monitor to ensure normal "flight operations." In addition, the subject must concurrently perform a psychomotor tracking task and respond to instructions to periodically change radio frequencies. This test yielded a variety of speed and accuracy scores for each subtask.

### Polysomnography

The sleep recordings were made while the aviator was sleeping in a darkened, private bedroom. Each night in which sleep was allowed, EOG and submental electrodes were placed, and the subject was escorted into his bedroom at 2250. Then the electrodes were plugged into the preamplifier, and the signal quality was checked. After the system was verified, the lights were turned out (at 2300) and the subject was permitted to sleep until 0630 while electrophysiological data were recorded. There were three nights during which polysomnographic data were collected. The first was a baseline night that occurred on Monday (following a Sunday adaptation night). The second was the recovery night on Wednesday, and the third was the recovery night on Friday. 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 stage 2 sleep, the percentage of time subjects spent in stages 1-4 and rapid eye movement (REM) sleep, the percentage of movement time, and the percentage of time subjects were awake during the night were calculated.

### Testing schedule

The subject reported to the laboratory on Sunday for medical examination, EEG electrode attachment, and an adaptation sleep period. On Monday, he received a small (2.5 mg) test dose of Dexedrine, and while he was being periodically monitored, he completed three training flights in the UH-60, each of which was followed by EEG, performance, mood, and CFF testing. Afterwards, he retired for the day. On Tuesday, there were three more test sessions (UH-60 flights, EEG, performance, mood, and CFF baseline tests), but the aviator was not allowed to go to sleep in the evening. Instead, he was given his first drug/placebo dose at 2400 hours and subsequent doses were given at 0400 and 0800 hours on Wednesday. On Wednesday, 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 for a total of five equally-spaced test sessions (at 0100, 0500, 0900, 1300, and 1700). Afterwards, the aviator retired for the day and his sleep was recorded. On Thursday, the aviator repeated the same schedule which was used on Tuesday--there were three test sessions during the day, and, as was the case on Tuesday night, he was not allowed to go to sleep. Instead he was given the first dose in his second series of drug/placebo doses at 2400. On Friday, the subject repeated the Wednesday schedule, beginning

with his first flight at 0100, and ending with a sleep period in the evening. On Saturday, the aviator was evaluated and released.

It should be noted that immediately prior to each drug/placebo dose, pulse and blood pressure (BP) were checked. In compliance with the safety limits set forth in the research protocol, the medical monitor would have been notified if the pulse had been greater than 100 beats per minute, or the systolic BP had been greater than 160 mmHg. A pulse greater than 120 beats per minute or a systolic BP of greater than 180 mmHg would have prevented the administration of Dexedrine during that test session; however, no pulse or blood pressure elevations exceeding these thresholds were detected.

## Results

### General

The primary purpose of this investigation was to establish the efficacy of Dexedrine for sustaining actual in-flight aviator performance despite moderate amounts of sleep loss, and to determine whether earlier findings from simulator studies could be replicated in a real aircraft. To accomplish these goals, the data from the two deprivation periods were analyzed to compare both the magnitude and time-course of Dexedrine's effects relative to placebo. Thus, the analyses evaluated the effects of the two primary factors of drug (Dexedrine versus placebo) and session (0100, 0500, 0900, 1300, and 1700).

### Flight performance

BMDP 4V (Dixon et al., 1990) was used to conduct a series of analyses of variance (ANOVAs) on the transformed RMS errors from each maneuver in the flight profile. The first two within-subjects factors for each maneuver were drug (placebo, Dexedrine) and session (0100, 0500, 0900, 1300, and 1700). Maneuvers which were flown more than once during each flight profile included a third factor designated iteration (there were four iterations of straight-and-levels, three right-standard-rate turns, and two left-standard-rate turns, descents, and climbs). Significant main effects and interactions from these ANOVAs were followed by appropriate posthoc analyses consisting of simple effects and/or contrasts to pinpoint the location of noteworthy differences. Because of the increase in error variance due to uncontrollable weather conditions in this study, the alpha level for reporting effects and rejecting the null hypothesis was set at .10 or below for the flight performance data.

### Straight and levels

The 3-way ANOVA (drug x session x iteration) conducted on heading, altitude, airspeed, slip, and roll control indicated an interaction between drug and iteration on heading RMS errors ( $F(1,9)=18.36, p=.0016$ ). Analysis of simple effects revealed this was due to the absence of a difference between the Dexedrine and placebo conditions during the first straight and level (SL), while there were significant differences between the two drug conditions during SLs 2-4 ( $p<.05$ ). In all three cases, heading control was better under Dexedrine than placebo. There was an especially large difference between the two drug conditions during SL 3 (see Figure 1).

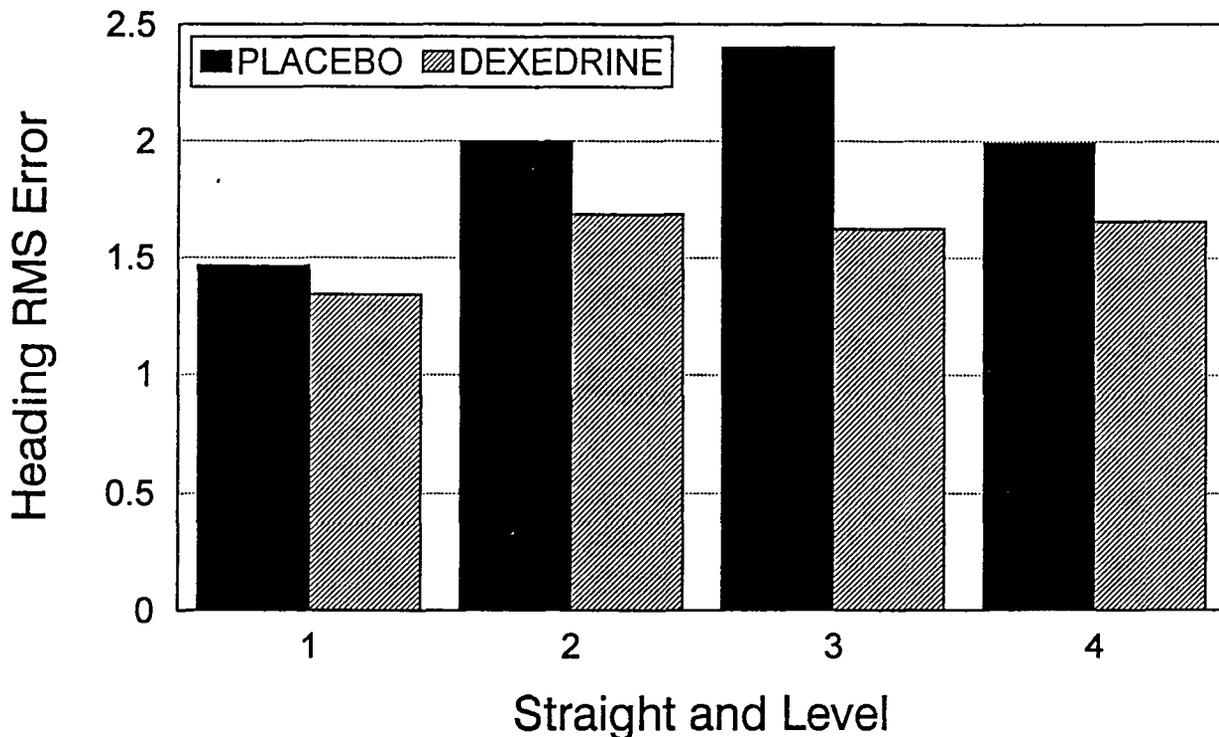


Figure 1. Effects of drug condition and maneuver iteration on heading errors during straight-and-level flight.

In addition to this 2-way interaction, there were several main effects. There were main effects on the iteration factor in terms of heading ( $F(5,27)=11.24, p=.0001$ ), altitude ( $F(5,27)=7.08, p=.0012$ ), airspeed ( $F(5,27)=5.38, p=.0049$ ), slip ( $F(5,27)=12.95, p<.0001$ ), and roll control ( $F(5,27)=9.97, p=.0001$ ). Pairwise comparisons indicated the effects on heading, airspeed, and roll were due to better performance on SL 1 than on SLs 2-4 ( $p<.05$ ). The effect on altitude was because of better performance on SLs 1, 2, and 4, than on SL 3, whereas the effect on slip control was because of better performance on SL 4 than on SLs 1, 2, and 3 and better performance on SL 1 than on SL 3 ( $p<.05$ ). These iteration effects (collapsed across drug condition) are depicted in figure 2. Main effects on the session factor were due to a general trend

towards better performance in the morning than in the afternoon. Specifically, heading errors were lower at 0100 than at 0500, 1300, and 1700, and they were lower at 0900 than at 1300 ( $p < .05$ ). Altitude control was better at 0100 than at 1300, and airspeed control was better at both 0100 and 0500 than it was at 0900 and 1300 ( $p < .05$ ). In addition, altitude control at 0900 was better than altitude control at 1300. The RMS errors for slip were lower in each of the three morning flights in comparison to the flight at 1300 ( $p < .05$ ). These session effects are depicted in figure 3.

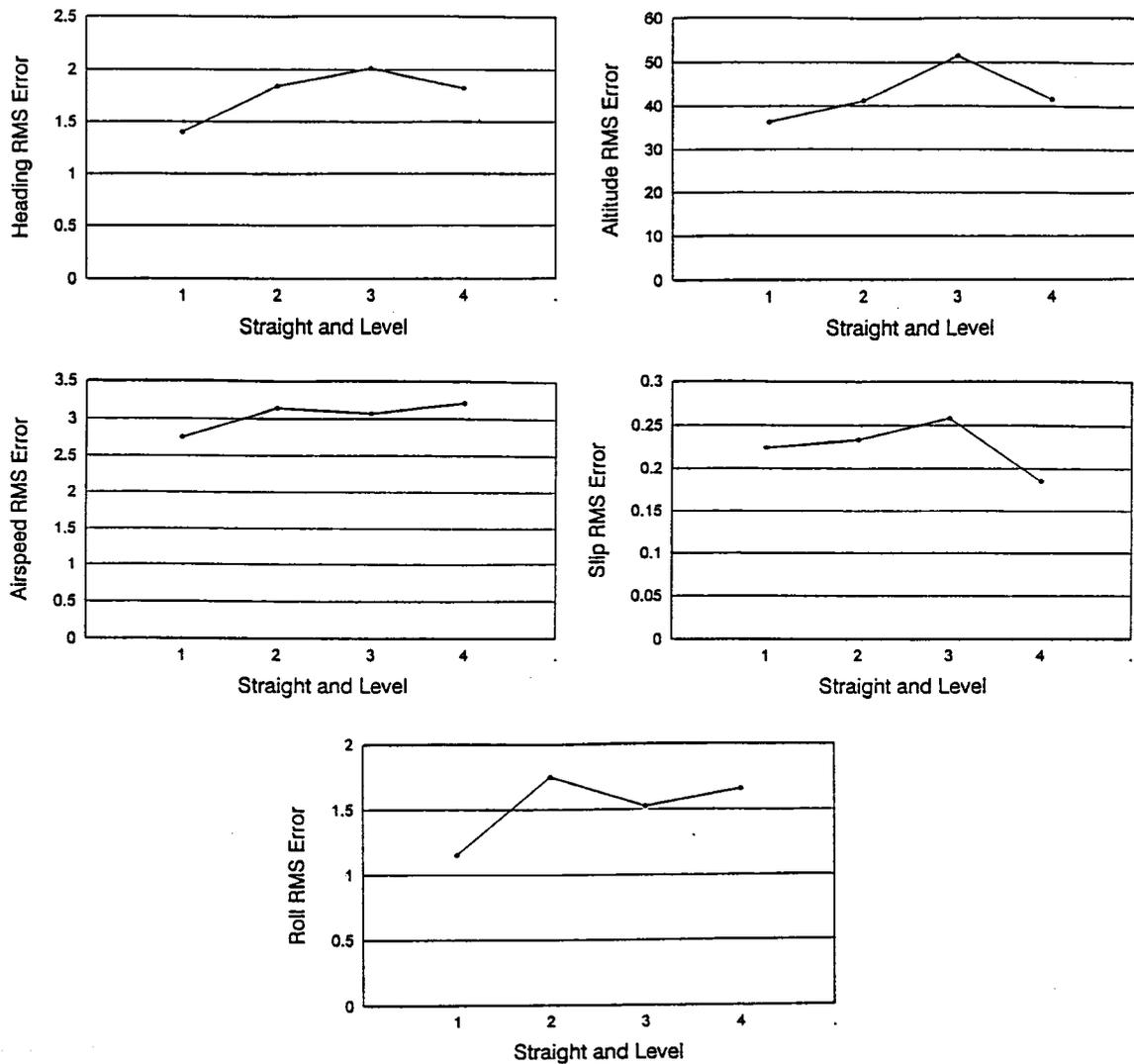


Figure 2. Effects of maneuver iteration on heading, altitude, airspeed, slip, and roll errors during straight-and-level flight.

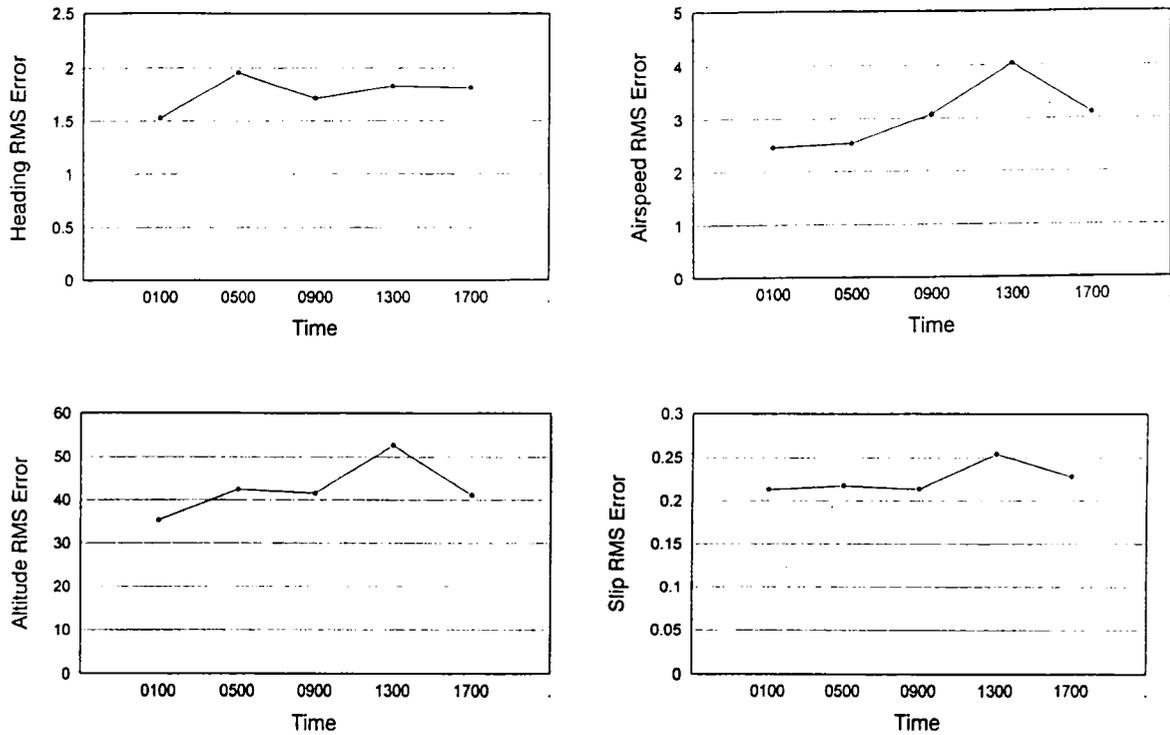


Figure 3. Effects of time of day on heading, airspeed, altitude, and slip errors during straight-and-level flight.

Two main effects on the drug factor indicated Dexedrine significantly reduced both heading errors ( $F(1,9)=19.79$ ,  $p=.0016$ ) and airspeed errors ( $F(1,9)= 5.24$ ,  $p=.0478$ ) during the flights. The RMS heading errors under Dexedrine versus placebo were 1.58 degrees and 1.96 degrees respectively, and the RMS airspeed errors were 2.9 knots and 3.2 knots.

#### Left standard-rate turns

The two left standard-rate turns (with AFCS and without AFCS) were analyzed in a 3-way ANOVA for drug, session, and iteration effects. The specific parameters evaluated were turn rate accuracy, and altitude, airspeed, slip, and roll control. The ANOVA indicated that, while there were no 3-way interactions, there was a marginal 2-way interaction on airspeed control ( $F(1,9)=4.37$ ,  $p=.0660$ ). Analysis of simple effects revealed this was due to better control under Dexedrine than placebo in the second ( $p<.07$ ), but not in the first turn (see figure 4).

There were significant main effects on the iteration, session, and drug factors. The ANOVA revealed that both airspeed ( $F(1,9)=13.80$ ,  $p=.0048$ ) and roll control ( $F(1,9)=17.11$ ,  $p=.0025$ ) were better during the first turn (with the AFCS) than during the second turn (without the AFCS). In addition, there were performance differences as a function of time of day as indicated by session main effects on altitude ( $F(4,36)=2.34$ ,  $p=.0733$ ), airspeed ( $F(4,36)=8.03$ ,  $p=.0001$ ), and slip control ( $F(4,36)=8.10$ ,  $p=.0001$ ). Generally, these were attributable to poorer performance at 1300 than elsewhere during the day. Altitude errors were higher at 1300 than

0900, and both airspeed and slip errors were greater at 1300 than at all of the other flights during the day ( $p < .05$ ). The differences in performance across flights are shown in figure 5.

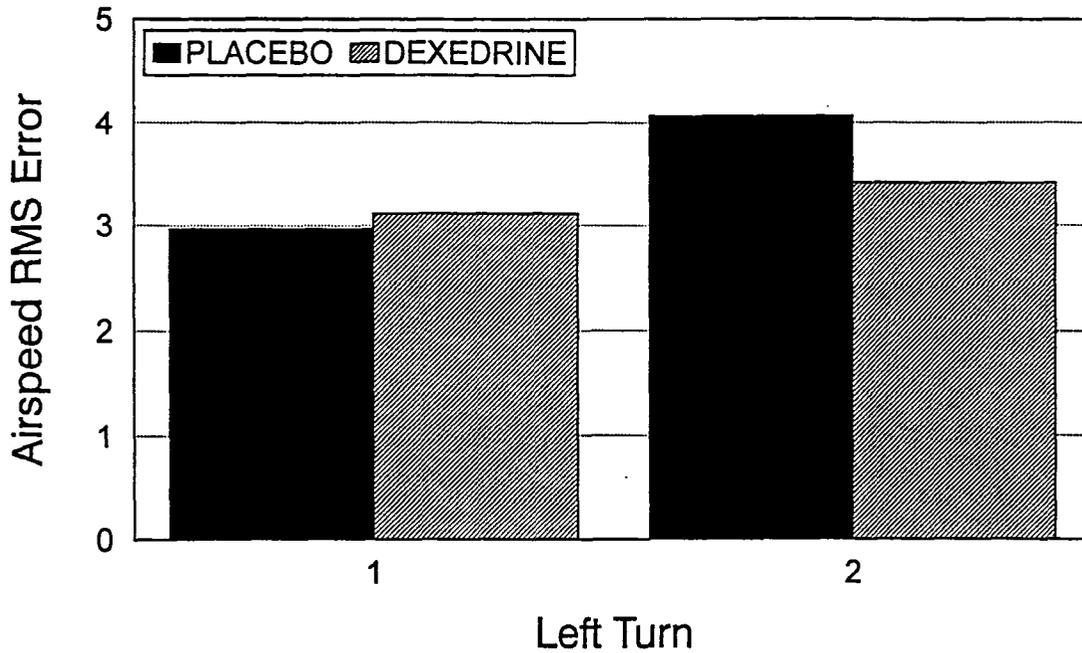


Figure 4. Effects of drug condition and maneuver iteration on airspeed errors during the left standard-rate turns.

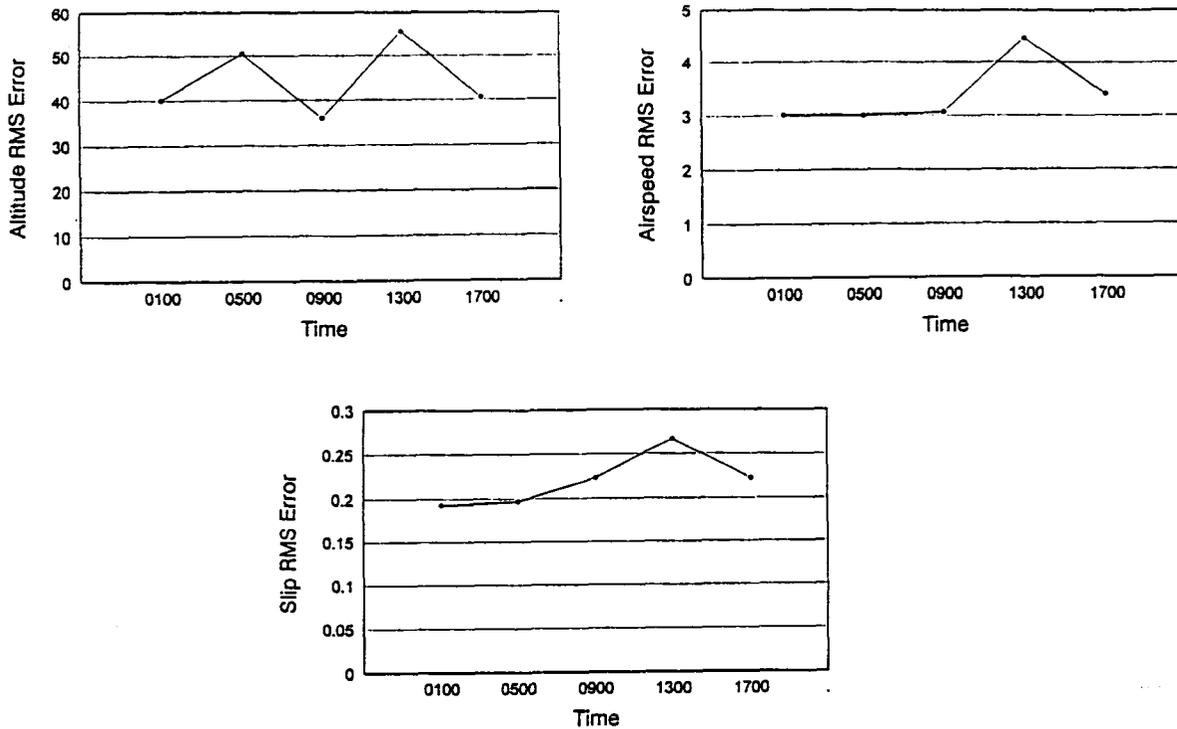


Figure 5. Effects of time of day on altitude, airspeed, and slip during the left standard-rate turns.

A drug main effect was found on roll control ( $F(1,9)=3.26, p=.1044$ ) because of better performance under Dexedrine than placebo. The mean RMS error under the two drug conditions were 1.7 degrees under Dexedrine versus 2.1 degrees under placebo.

### Climbs

There were two standard-rate climbs (both flown with the AFCS engaged) which were analyzed in a 3-way ANOVA for drug, session, and iteration. The analysis indicated a drug-by-iteration interaction on vertical speed control ( $F(1,9)=5.35, p=.0461$ ), which subsequently was found to be due to better performance under placebo than Dexedrine during the first ( $p<.05$ ), but not the second climb (see figure 6).

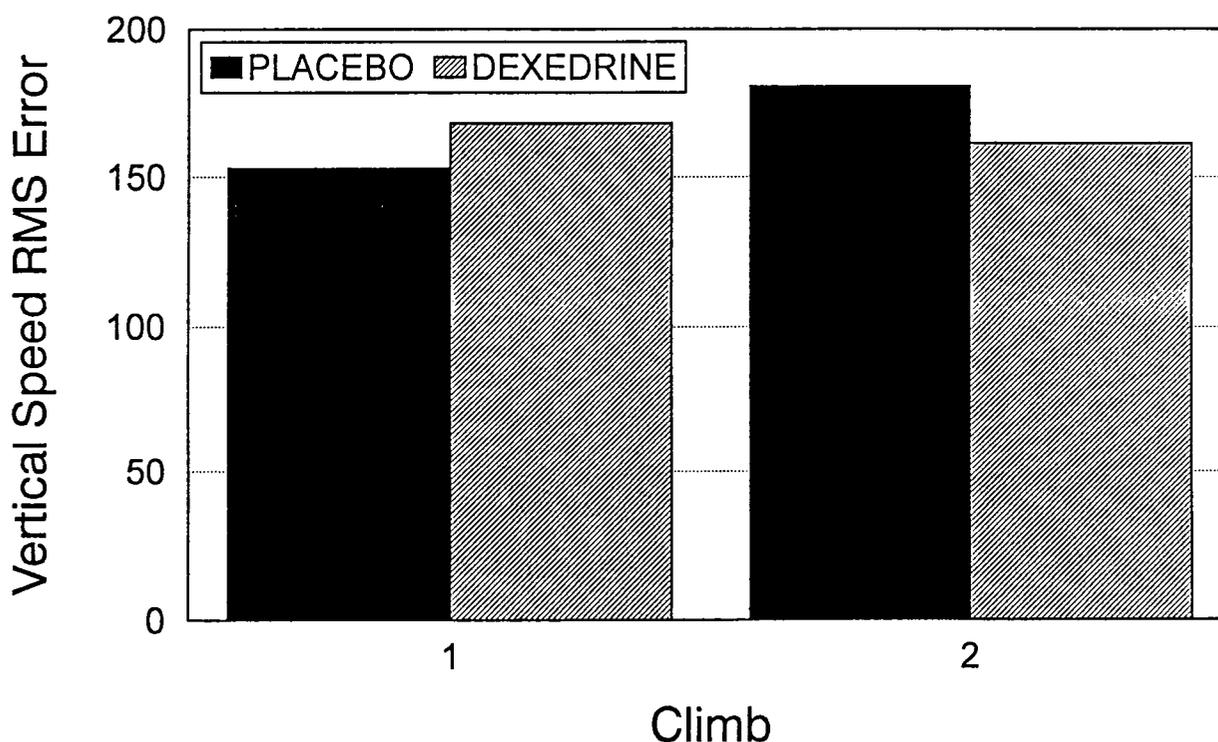


Figure 6. Effects of drug condition and maneuver iteration on vertical speed errors during the climbs.

There were main effects on the iteration, session, and drug factors. The iteration effect was found on heading control ( $F(1,9)=9.47, p=.0132$ ), and inspection of the mean performance under both climbs indicated this was because of better performance on the first climb than on the second climb. The difference may have resulted from the fact that the second climb was the longer of the two (120 seconds versus 60 seconds). The session main effects were found on airspeed ( $F(4,36)=11.15, p<.0001$ ), slip ( $F(4,36)=5.71, p=.0012$ ), roll ( $F(4,36)=2.36, p=.0716$ ), and vertical speed control ( $F(4,36)=25.59, p<.0001$ ). Generally, these were attributable to better

performance on the earlier as opposed to the later flights in each day. Contrasts on airspeed RMS errors revealed more precise control at 0100, 0500, 0900, and 1700 than at 1300 ( $p < .05$ ). In addition, airspeed control was better at 0100 than at 1700. Slip control was better at both 0500 and 0900 than at 1300 and 1700, and slip control was more precise at 0500 than at 0100 ( $p < .05$ ). Roll control was substantially better both at 0500 and 1300 than it was at 1700 ( $p < .05$ ). Lastly, vertical speed RMS errors were smaller at 0100 and 0500 than they were at 1300 and 1700, smaller at 0500 than at 0900, smaller at 0900 than at 1300, but larger at 1300 than at 1700 ( $p < .05$ ). These differences are shown in figure 7.

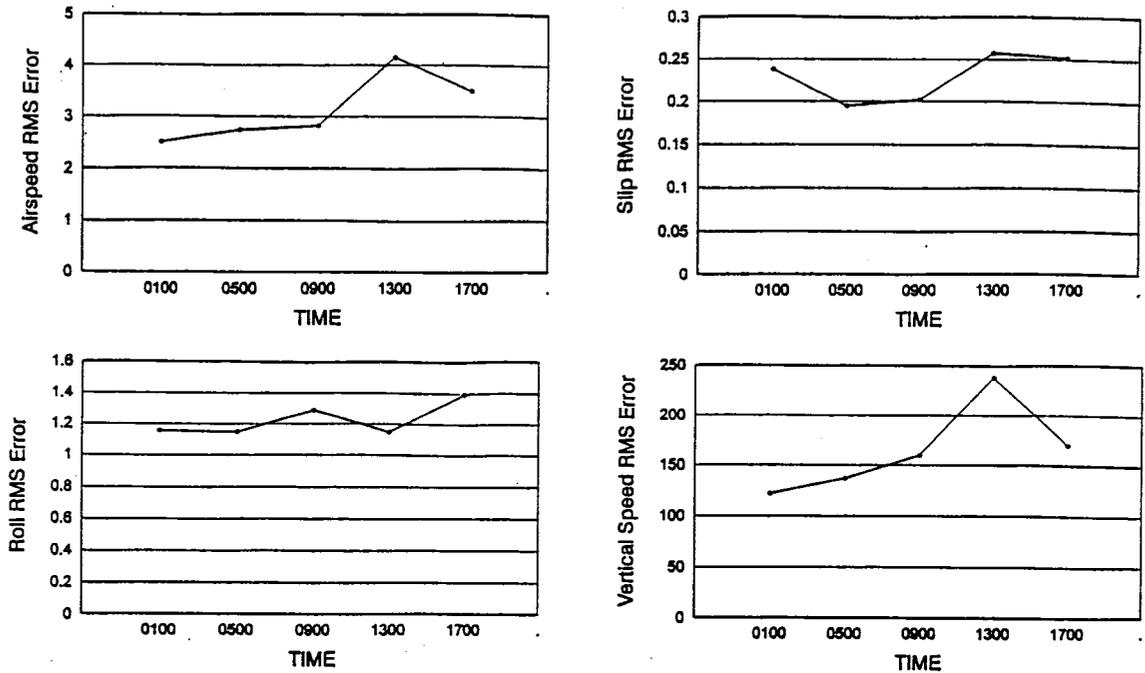


Figure 7. Effects of time of day on airspeed, slip, roll, and vertical speed errors during climbs.

Main effects on the drug factor were found on both heading control ( $F(1,9)=6.36, p=.0164$ ) and slip control ( $F(1,9)=6.02, p=.0365$ ). The differences between Dexedrine and placebo were 1.5 versus 1.7 degrees for heading and .21 versus .25 ball widths for slip.

### Right standard-rate turns

The three right standard-rate turns (the first two with the AFCS) were examined with regard to turn rate, altitude, airspeed, slip, and roll control using a 3-way ANOVA. The analysis indicated a 2-way interaction between drug and iteration on roll control ( $F(2,18)=3.54, p=.0506$ ). Analysis of simple effects revealed this was due to better performance under Dexedrine than placebo during the third turn (without the AFCS), but not during the first and second turns ( $p < .05$ ). This interaction is shown in figure 8.

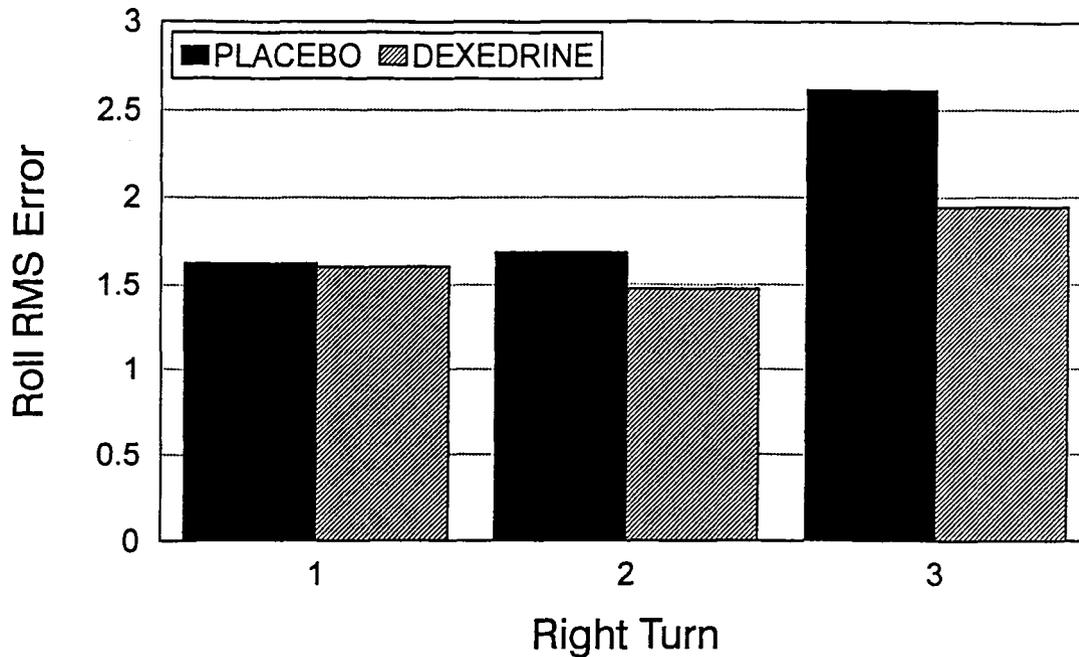


Figure 8. Effects of drug and iteration on roll errors during the right standard-rate turns.

There were no drug main effects on any of the five control parameters studied; however, there were main effects on both the iteration and session factors. The iteration effect was related to roll control differences among the three turns ( $F(2,18)=12.09$ ,  $p=.0005$ ) which contrasts indicated was due to the fact that RMS errors were higher on the third turn than on the first or second ( $p<.05$ ). The session effects were found on altitude ( $F(4,36)=4.60$ ,  $p=.0042$ ) and airspeed control ( $F(4,36)=11.83$ ,  $p<.0001$ ). Altitude RMS errors were smaller at 0100 than at any of the remaining sessions ( $p<.05$  for all except 0100 versus 0500 where  $p<.07$ ). Airspeed errors also were smaller at 0100 than elsewhere, but in addition, they were significantly larger at 1300 than at the other times ( $p<.05$ ). These differences are depicted in figure 9.

### Descents

The analysis of heading, airspeed, slip, roll, and vertical speed control during the two descents (both without the AFCS) indicated no interactions, but several main effects. There were iteration effects on heading ( $F(1,9)=3.88$ ,  $p=.0803$ ) and roll control ( $F(1,9)=17.34$ ,  $p=.0024$ ), both of which were due to better performance on the first as opposed to the second descent. There were session main effects on both slip ( $F(4,36)=3.89$ ,  $p=.0100$ ) and vertical speed control ( $F(4,36)=6.53$ ,  $p=.0005$ ). Slip errors were larger at 1300 than at 0100, 0500, 0900, or 1700, and vertical speed errors were larger at 1300 than at 0100, 0500, and 1700, and larger at 0900 than at 0100 ( $p<.05$ ). These differences are shown in figure 10.

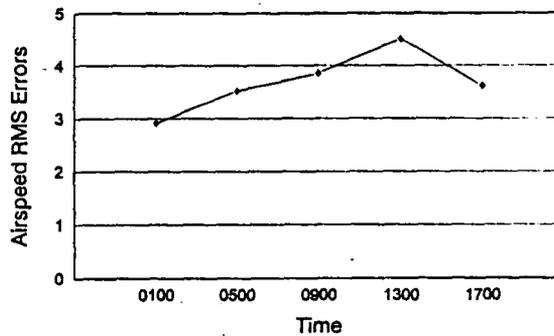
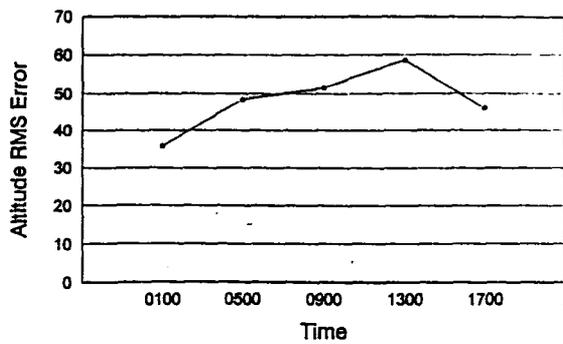


Figure 9. Effects of time of day on altitude and airspeed during the right standard-rate turns.

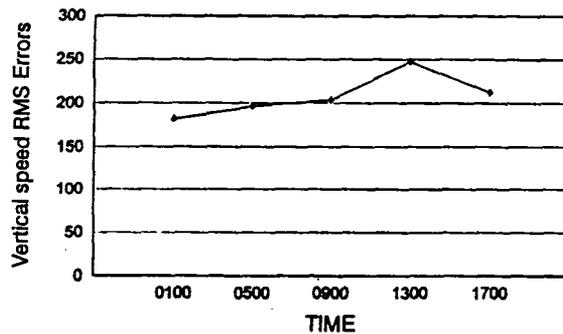
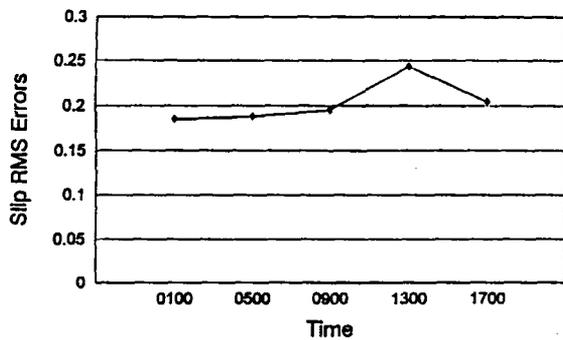


Figure 10. Effects of time of day on slip and vertical speed errors during the descents.

There were several main effects attributable to the effects of the drug conditions as well. RMS errors for heading ( $F(1,9)=5.64, p=.0415$ ), airspeed ( $F(1,9)=5.44, p=.0445$ ), roll ( $F(1,9)=9.98, p=.0116$ ), and vertical speed control ( $F(1,9)=9.90, p=.0036$ ) all were lower under the Dexedrine condition than the placebo condition. The means for Dexedrine versus placebo were 1.6 versus 1.8 degrees of heading, 3.0 versus 3.4 knots of airspeed, 1.3 versus 1.6 degrees of roll, and 192 versus 224 feet per minute of vertical speed.

### Left descending turn

The single left descending turn (conducted without the AFCS) during each flight was analyzed in terms of turn rate, airspeed, slip, roll, and vertical speed control. The 2-way ANOVA indicated two drug-by-session interactions and three main effects. The interactions were found on the roll ( $F(4,36)=2.87, p=.0369$ ) and vertical speed ( $F(4,36)=3.98, p=.0090$ ) measures. Analysis of simple effects indicated that roll control was more precise under Dexedrine than placebo at the 0900 flight ( $p<.05$ ), but not at the others. Vertical speed control also was better under Dexedrine versus placebo at 0500, but performance remained better at 0900 as well ( $p<.05$ ). These effects are depicted in figure 11.

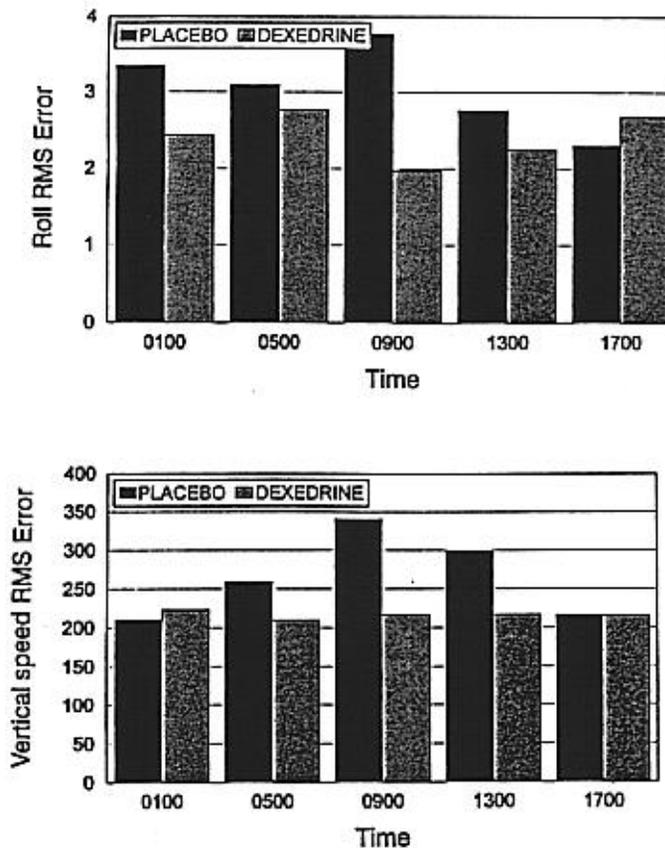


Figure 11. Effects of drug and time of day on roll and vertical speed errors during the left descending turn.

Differences among the various sessions, regardless of drug condition, were found on both slip ( $F(4,36)=6.66$ ,  $p=.0004$ ) and vertical speed control ( $F(4,36)=3.55$ ,  $p=.0154$ ). Subsequent contrasts indicated the slip effect was attributable to greater errors at 1300 than at the other times of the day ( $p<.05$ ). A similar effect occurred on vertical speed control, but in this case the 1300 flight was significantly worse than all of the other flights with the exception of the one at 0900, but the 0900 flight was significantly worse than the 0100 flight ( $p<.05$ ). The session differences are shown in figure 12.

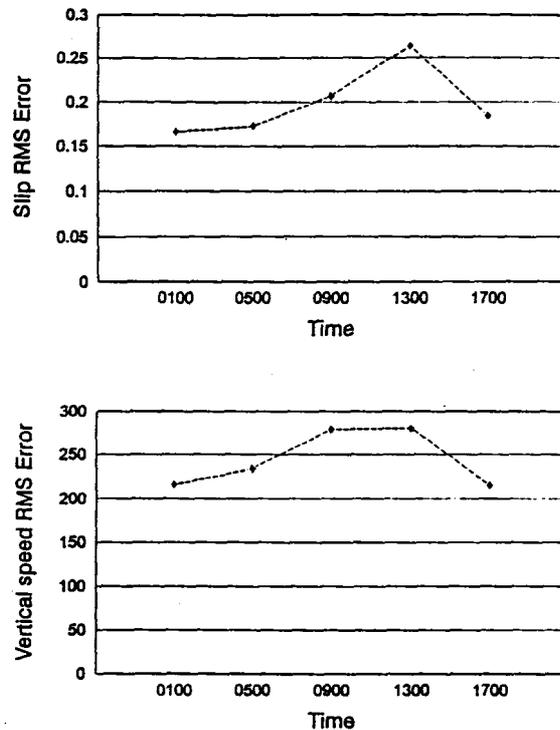


Figure 12. Effects of time of day on slip and roll errors during the left descending turn.

A drug main effect was found on vertical speed control ( $F(1,9)=7.12$ ,  $p=.0257$ ) because of better performance under Dexedrine than placebo. The RMS error means for the two drug conditions (Dexedrine and placebo) were 225 versus 264 feet per minute.

### ILS approach

Performance during the ILS was assessed in terms of airspeed, slip, and roll control, and localizer and glideslope tracking accuracy. The 2-way ANOVA revealed there were two drug-by-session interactions on this maneuver. The first was an interaction on slip control ( $F(4,36)=2.94$ ,  $p=.0336$ ) which was found to be due to larger slip errors under the Dexedrine than the placebo condition at 0500 ( $p<.05$ ). The second was an interaction on glideslope control

( $F(4,36)=2.19, p=.0893$ ), but this was found to be due to better control under Dexedrine than placebo at 1300 ( $p<.05$ ). Both interactions are depicted in figure 13.

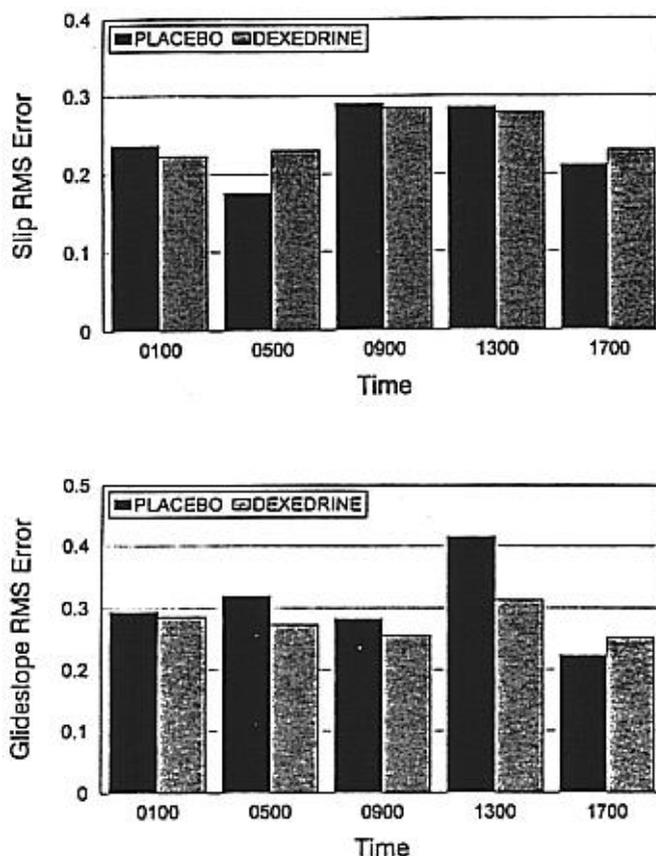


Figure 13. Effects of drug and time of day on slip and glideslope errors during the ILS.

There were session main effects on all of the measures examined: airspeed ( $F(4,36)=6.04, p=.0008$ ), slip ( $F(4,36)=7.43, p=.0002$ ), roll ( $F(4,36)=5.32, p=.0018$ ), localizer ( $F(4,36)=4.31, p=.0060$ ), and glideslope ( $F(4,36)=7.16, p=.0002$ ). Generally, these were due to better performance in the mornings than in the early afternoon; however, there were exceptions. Both airspeed and slip control were better at 0100 and 0500 than at 0900 and 1300, but airspeed control was better at 1700 than at 1300 as well, whereas slip control was better at 1700 than at both 1300 and 0900 ( $p<.05$ ). Roll control was more precise at the beginning of the day (at 0100) and at the end of the day (at 1700) than at 0500 and 0900 ( $p<.05$ ). Localizer tracking improved throughout the test days as evidenced by greater errors at 0100, 0500, and 0900 than at 1700. In addition, performance was poorest at 0500 in comparison to all of the other times with the exception of 1300 ( $p<.05$ ). Last, glideslope control was significantly worse at 1300 than it was at all of the other times of day ( $p<.05$ ). These session effects are shown in figure 14.

There was a main effect on the drug factor for localizer tracking ( $F(1,9)=3.98, p=.0773$ ) which was due to more precise tracking under Dexedrine than placebo. The mean RMS errors were 1.12 under Dexedrine versus 1.36 under placebo.

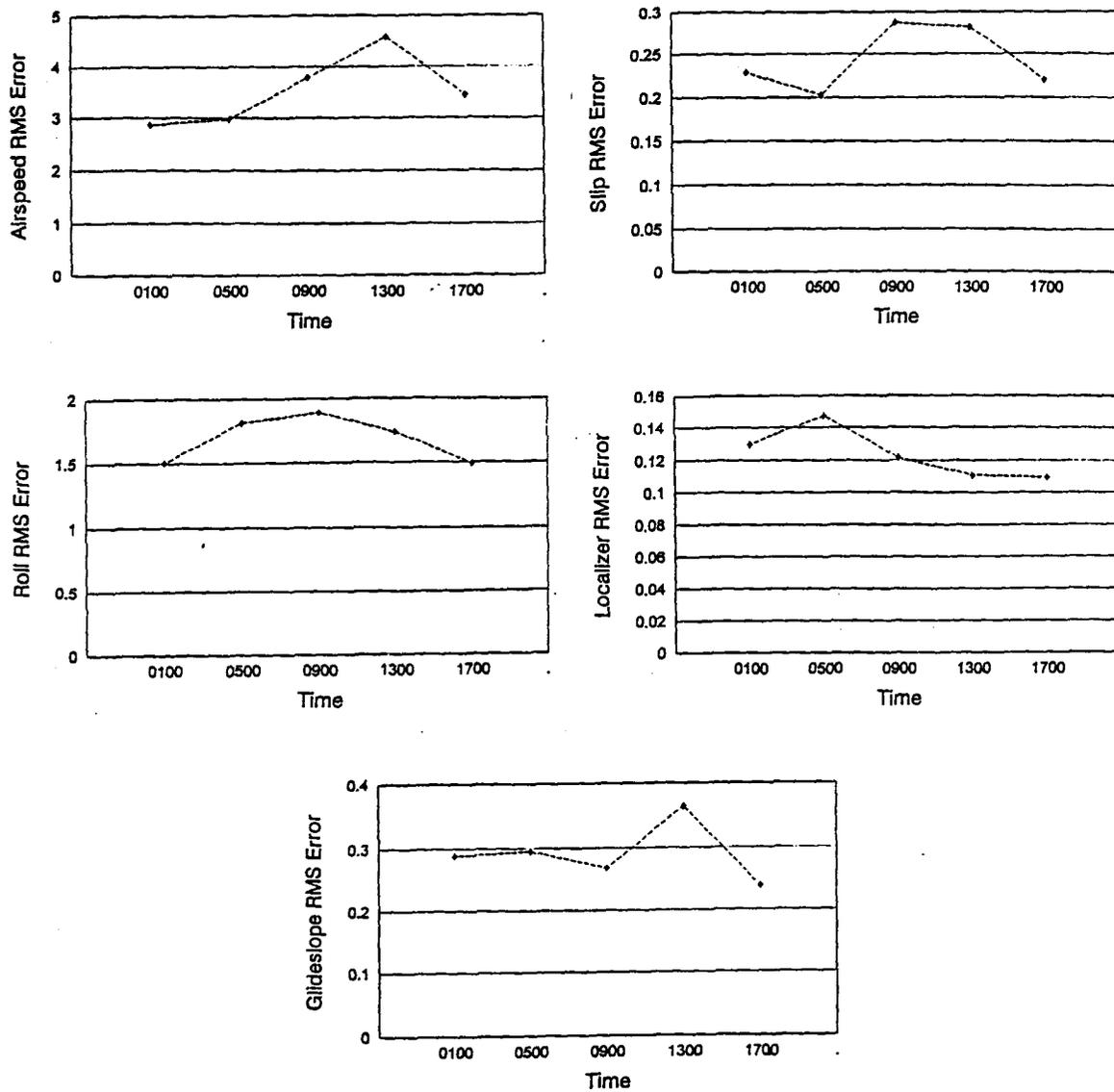


Figure 14. Effects of time of day on airspeed, slip, roll, localizer, and glideslope during the ILS.

### Electroencephalographic activity

The absolute power values from the resting EEGs were analyzed with BMDP 4V repeated measures ANOVA (Dixon et al, 1990) to determine the effects of drug (placebo, Dexedrine), session (0220, 0620, 1020, 1420, and 1820), and eyes (closed, open) at Fz, C3, Cz, C4, Pz, O1, and O2. Significant effects were followed up with appropriate analyses of simple effects and/or contrasts to pinpoint the location of noteworthy differences.

### Delta activity

The analysis of delta activity (1.5-3.0 Hz) indicated there were no significant interactions or other drug-related effects. Only tendencies toward increases in delta activity under placebo relative to Dexedrine were observed at Fz, Cz, C4, and C3 ( $p < .10$ ); however, none of these were statistically significant.

There were several main effects attributable to whether or not the subjects had their eyes open or closed. At Fz ( $F(1,9)=12.25, p=.0067$ ), C3 ( $F(1,9)=8.63, p=.0166$ ), Cz ( $F(1,9)=9.58, p=.0128$ ), Pz ( $F(1,9)=9.70, p=.0124$ ), O1 ( $F(1,9)=18.81, p=.0019$ ), and O2 ( $F(1,9)=17.33, p=.0024$ ) there was more delta activity with eyes closed than with eyes opened.

### Theta activity

The 3-way ANOVA on theta activity (3.0-8.0 Hz) revealed drug-by-eyes interactions at Fz ( $F(1,9)=9.14, p=.0144$ ), C3 ( $F(1,9)=6.41, p=.0321$ ), Cz ( $F(1,9)=8.74, p=.0161$ ), C4 ( $F(1,9)=7.56, p=.0225$ ), and marginally at Pz ( $F(1,9)=4.80, p=.0562$ ). All of these were found to be due to elevations in theta activity under placebo compared to Dexedrine during eyes closed ( $p < .05$ ), as can be seen in figure 15.

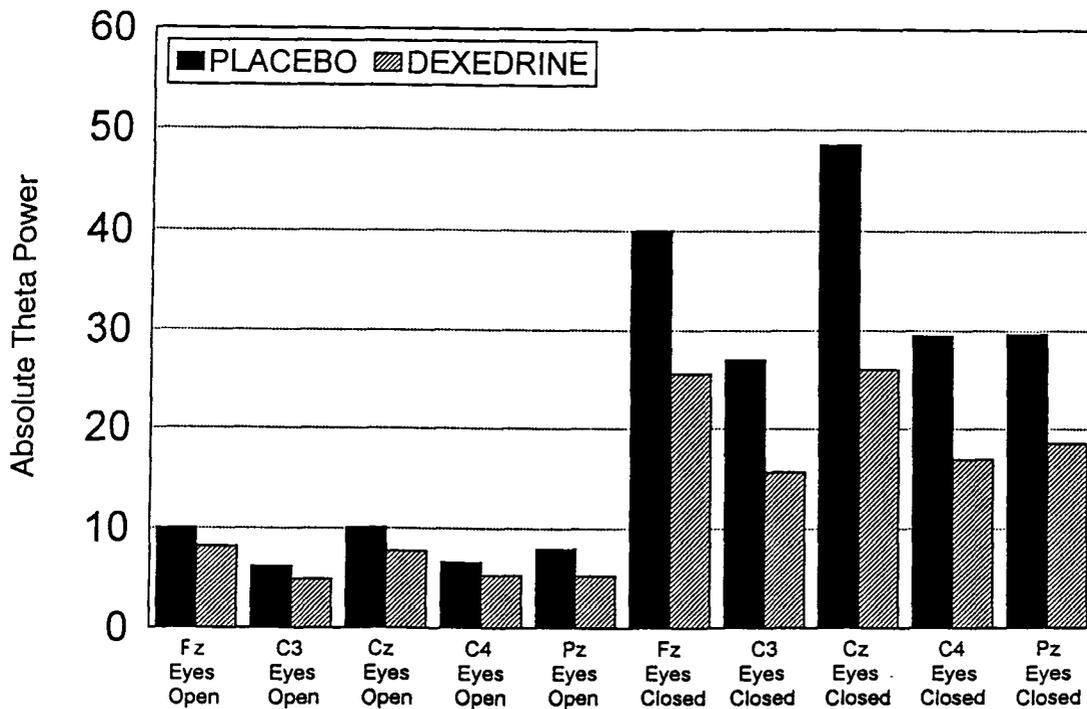


Figure 15. Effects of drug and eye closure on EEG theta activity.

There also were main effects on the eyes factor at Fz ( $F(1,9)=18.80, p=.0019$ ), C3 ( $F(1,9)=39.64, p=.0001$ ), Cz ( $F(1,9)=30.04, p=.0004$ ), C4 ( $F(1,9)=28.99, p=.0004$ ), Pz ( $F(1,9)=25.16, p=.0007$ ), O1 ( $F(1,9)=27.03, p=.0006$ ), and O2 ( $F(1,9)=16.17, p=.0030$ ). Examination of mean theta power as a function of eye closure at these electrode sites indicated there was more theta at eyes closed than at eyes open in every case.

Drug main effects, consistent with what was observed in the drug-by-eyes interactions were found at C3 ( $F(1,9)=7.84, p=.0207$ ), Cz ( $F(1,9)=8.45, p=.0174$ ), C4 ( $F(1,9)=6.72, p=.0291$ ), and Pz ( $F(1,9)=6.04, p=.0363$ ). All of these differences were due to elevations in theta activity under placebo in comparison to Dexedrine.

### Alpha activity

The analysis of alpha activity (8.0-13.0 Hz) indicated drug-by-eyes interactions at C4 ( $F(1,9)=7.93, p=.0202$ ), Cz ( $F(1,9)=8.40, p=.0177$ ), Fz ( $F(1,9)=11.80, p=.0074$ ), and O2 ( $F(1,9)=6.38, p=.0325$ ), all of which were due to increases in alpha activity under Dexedrine in comparison to placebo during eyes closed ( $p<.05$ ). These effects are depicted in figure 16.

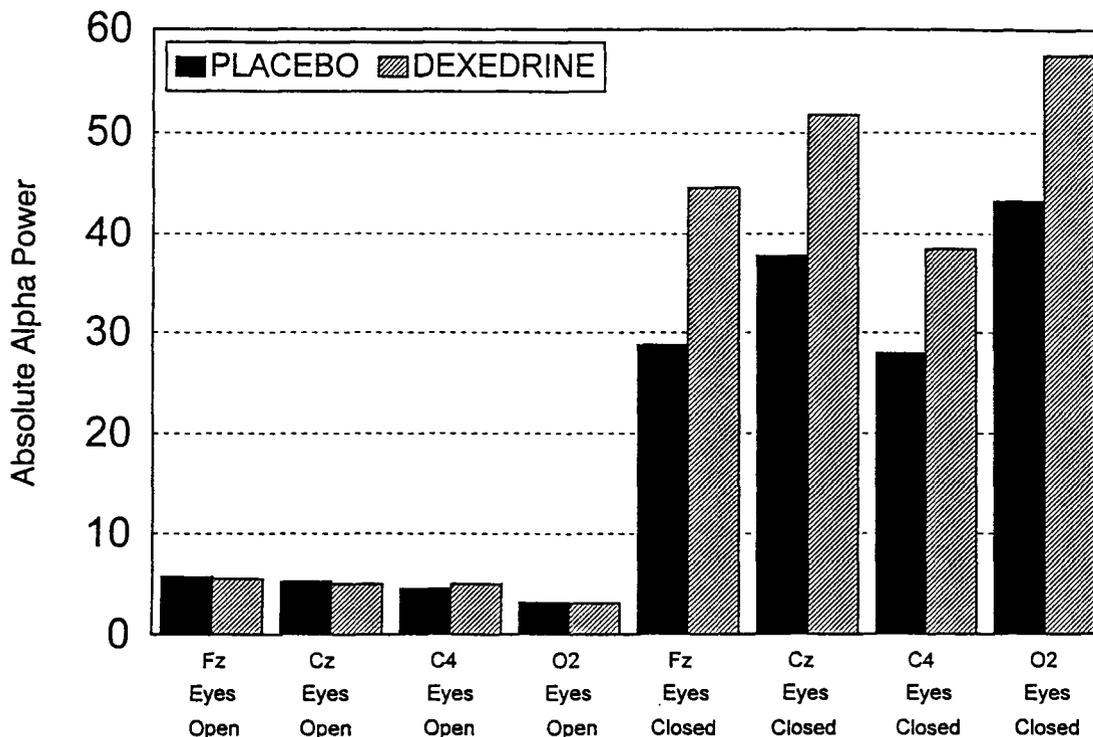


Figure 16. Effects of drug and eye closure on EEG alpha power.

There were main effects on the eyes factor at Fz ( $F(1,9)=7.88, p=.0204$ ), Cz ( $F(1,9)=6.12, p=.0353$ ), C4 ( $F(1,9)=5.56, p=.0427$ ), O1 ( $F(1,9)=7.59, p=.0223$ ), O2 ( $F(1,9)=8.23, p=.0185$ ),

and marginally at Pz ( $F(1,9)=4.71, p=.0582$ ). All were due to increases in alpha power at eyes closed in comparison to eyes open.

In addition, there were drug main effects at Fz ( $F(1,9)=9.93, p=.0117$ ), Cz ( $F(1,9)=6.51, p=.0311$ ), C4 ( $F(1,9)=7.01, p=.0266$ ), and O2 ( $F(1,9)=6.36, p=.0327$ ). Consistent with what was observed in the drug-by-eyes interaction, all of these were a result of greater alpha power under Dexedrine than placebo.

### Beta activity

The 3-way ANOVA on beta activity (13.0-20.0 Hz) revealed there were no drug-related effects. However, there was one session-by-eyes interaction, and several main effects on the eyes factor. The interaction was found at O1 ( $F(4,36)=3.48, p=.0168$ ), and analysis of simple effects indicated that, although there was more beta at eyes closed than eyes open during every test session, the difference was larger at 0215 than elsewhere.

Main effects on the eyes factor were found at Fz ( $F(1,9)=24.83, p=.0008$ ), C3 ( $F(1,9)=9.22, p=.0141$ ), Cz ( $F(1,9)=13.20, p=.0055$ ), C4 ( $F(1,9)=10.85, p=.0093$ ), Pz ( $F(1,9)=9.16, p=.0143$ ), O1 ( $F(1,9)=12.30, p=.0067$ ), and O2 ( $F(1,9)=13.31, p=.0053$ ). All of these effects were due to an increase in beta activity under eyes closed versus eyes open.

### Desktop flight simulator

Data collected on the desktop flight simulator consisted of 1) a score reflecting the accuracy with which subjects “flew” a simulated course and 2) a speed measure. These data were analyzed with BMDP 4V (Dixon et al., 1990) for drug (placebo, Dexedrine) and session (0250, 0650, 1050, 1450, and 1850) effects. The ANOVA revealed that there were no significant interactions or main effects on this task, potentially due to excessive variability introduced by learning effects and the fact that missed “gates” in the course often caused a subject to earn a score that departed substantially from all of his others.

### POMS

Data were collected on the POMS during each of the five sessions on both deprivation days and immediately prior to and following these five sessions. Thus, the data for each of the 6 scales were analyzed using BMDP 4V (Dixon et al., 1990) repeated measures analysis of variance in which the factors were drug (Dexedrine, placebo) and session (2340, 0325, 0725, 1125, 1525, 1925, and 2225).

### 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. In addition, although the session main effect approached significance at  $p=.08$ , there were no marked differences in tension-anxiety scores as a function of time of day.

### Depression-dejection scale

The scores on the depression-dejection scale, which measures despondence and sadness, indicated a drug-by-session interaction ( $F(6,54)=2.92, p=.0155$ ), but no drug or session main effect. As can be seen in figure 17, the interaction was due to significantly more depression under the placebo relative to the Dexedrine condition at 0725 ( $p<.05$ ), whereas there were no drug-related differences at the other times.

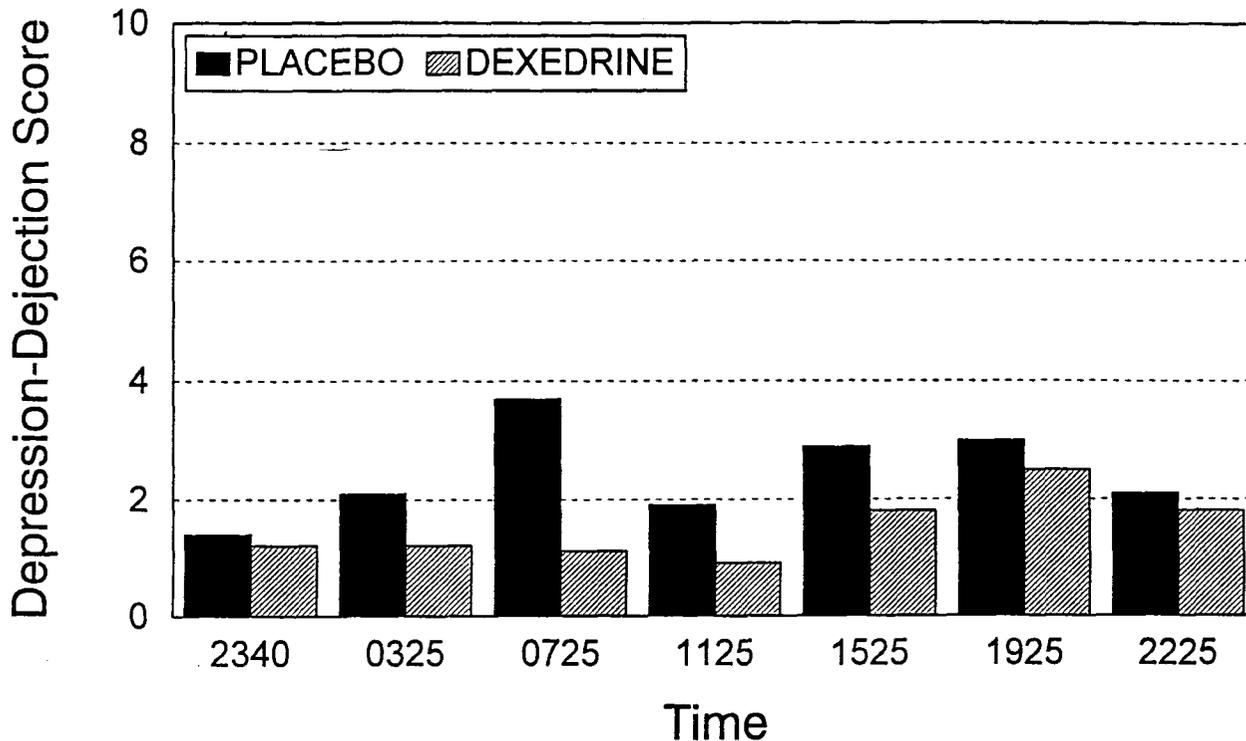


Figure 17. Effects of drug and time of day on POMS depression-dejection ratings.

### Anger-hostility scale

The 2-way ANOVA on anger-hostility scores, which reflect anger and antipathy towards others, indicated no significant main effects or interactions.

## Vigor-activity scale

The ANOVA on vigor-activity scores, which reflect high energy levels, revealed several effects. There was a drug-by-session interaction ( $F(6,54)=5.05$ ,  $p=.0004$ ) which analysis of simple effects indicated was due to substantially lower vigor scores under placebo than under Dexedrine at 0325, 0725, 1125, and 1925 ( $p<.05$ ), whereas there were no differences between the two drug conditions at 2340 (before deprivation) or at 2225 (at the end of deprivation). This interaction is depicted in figure 18. In addition, there was a session main effect ( $F(6,54)=5.54$ ,  $p=.0002$ ). Although in the presence of a higher-order interaction, this effect must be interpreted cautiously, subsequent pairwise contrasts revealed that overall vigor scores peaked at 0325 and then dropped throughout the remainder of the day. Specifically, the 2340 score was higher than the 2225 score, and the 0325 score was higher than all of the remaining scores with the exception of the one at 1125 ( $p<.05$ ). In addition, the 1125 score was greater than the ones at 0725, 1525, 1925, and 2225 ( $p<.05$ ). These session effects are shown in figure 19. The drug main effect ( $F(1,9)=46.50$ ,  $p=.0001$ ) was due to an overall reduction in vigor ratings under the placebo versus the Dexedrine condition. The mean vigor activity ratings were 10.7 for placebo and 17.6 for Dexedrine.

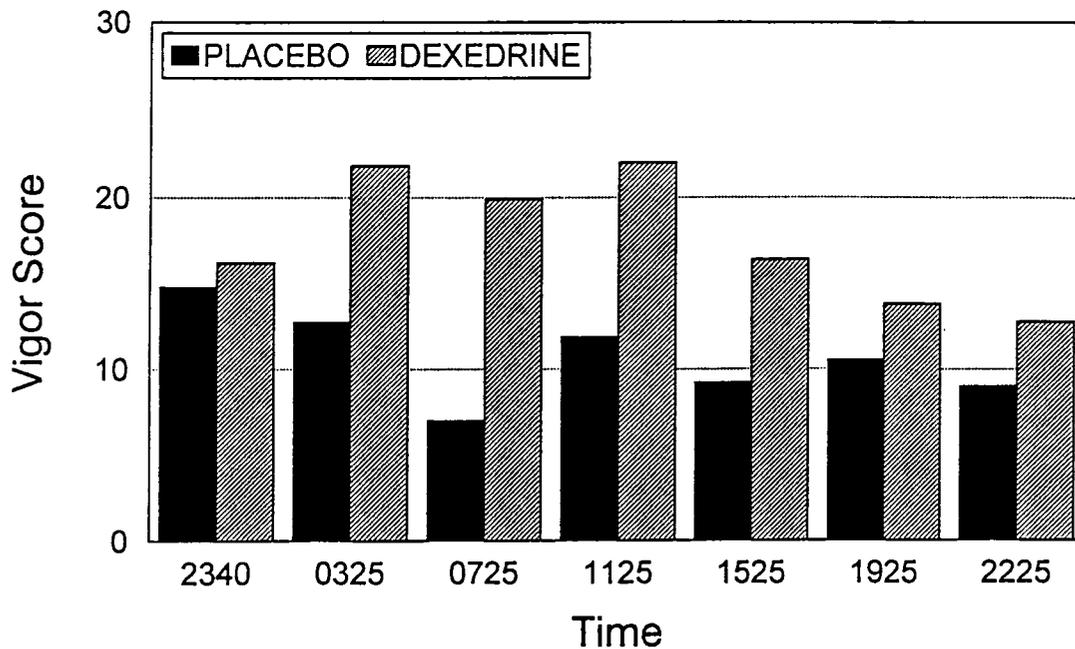


Figure 18. Effects of drug and time of day on POMS vigor-activity ratings.

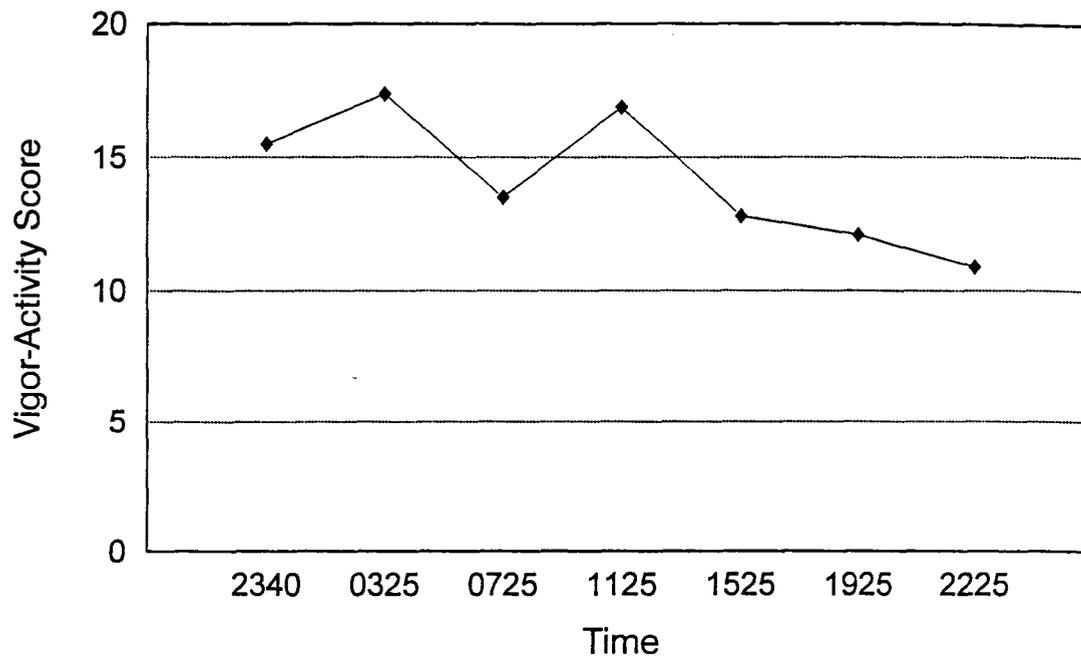


Figure 19. Effects of time of day on POMS vigor-activity ratings.

#### Fatigue-inertia scale

The 2-way ANOVA on fatigue-inertia scores, which signify increases in weariness and tiredness, showed there was a significant interaction between drug and session ( $F(6,54)=2.75$ ,  $p=.0210$ ), a significant main effect on the session factor ( $F(6,54)=5.00$ ,  $p=.0004$ ), and a significant effect on the drug factor ( $F(1,9)=28.20$ ,  $p=.0005$ ). As shown in figure 20, the interaction was due to higher levels of fatigue under placebo than Dexedrine at 0325, 0725, 1125, and 2225 ( $p<.05$ ), while there were no differences between the drug conditions at the other times of the day. The overall session effect indicated lower subjective perceptions of fatigue at 2340 than at 0725, 1525, or 1925; lower fatigue levels at 0325 than at 0725 or 2225; and a slight dip in fatigue ratings at 1125 in comparison to all of the sessions from 0725 until the end of the day ( $p<.05$ ). This effect is shown in figure 21. 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 11.9 versus 6.3).

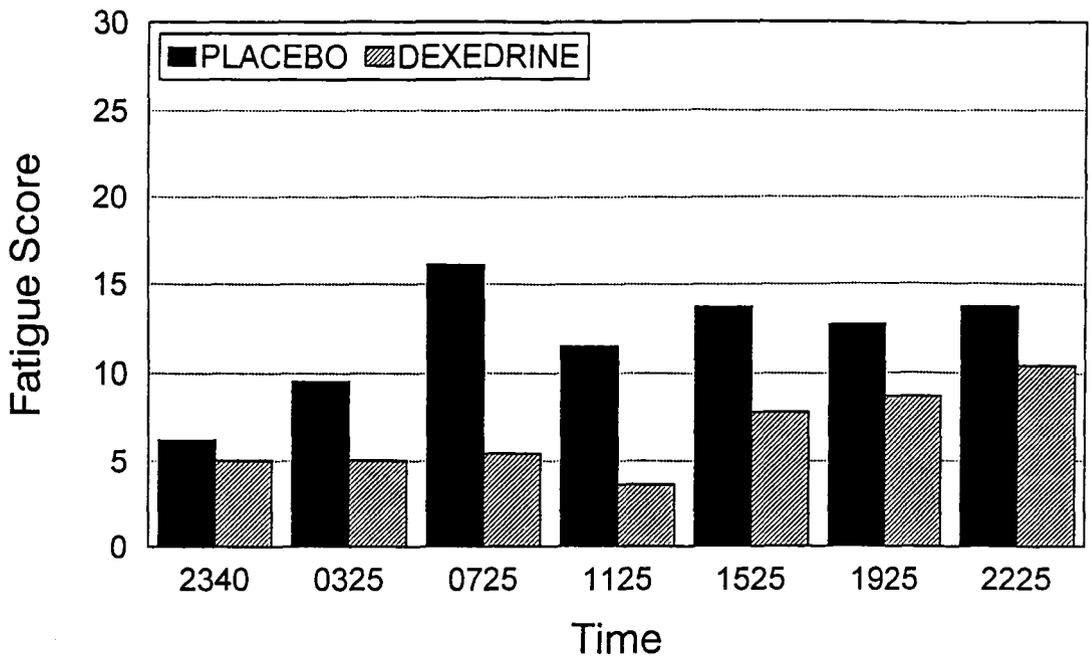


Figure 20. Effects of drug and time of day on POMS fatigue-inertia ratings.

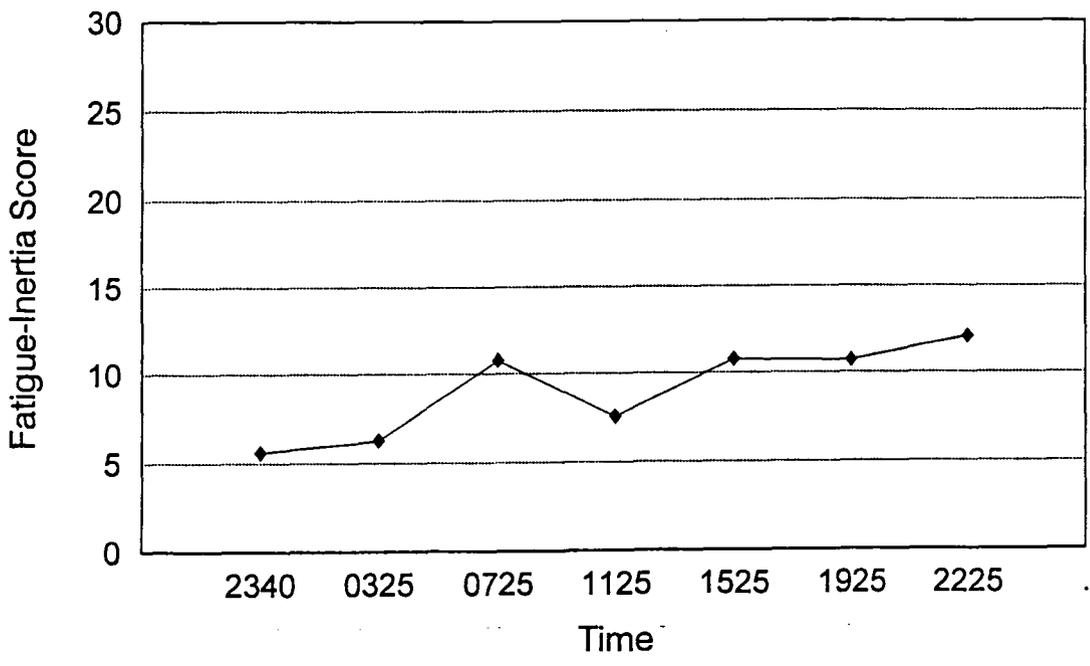


Figure 21. Effects of time of day on POMS fatigue-inertia ratings.

### Confusion-bewilderment scale

Analysis of the confusion-bewilderment scores, which reflect increased difficulties in mental abilities, showed several effects consistent with those seen in the previous two scales. Specifically, there was a drug-by-session interaction ( $F(6,54)=4.83, p=.0005$ ), a session main effect ( $F(6,54)=3.11, p=.0108$ ), and a drug main effect ( $F(1,9)=33.51, p=.0003$ ). The interaction was due to significantly higher confusion scores under placebo than Dexedrine at 0325, 0725, and 1125 ( $p<.05$ ), but not at the other times of the day (see figure 22). The session effect was because confusion scores at 2340 were smaller than those at 0725 ( $p<.05$ ) and 1525 ( $p<.06$ ). In addition, these scores were smaller at 0325 than at 0725, and they were smaller at 1125 than at 0725, 1525, and 2225 ( $p<.05$ ) as can be seen in figure 23. The drug main effect was attributable to the general reduction in self-perceptions of confusion which occurred under Dexedrine in comparison to placebo (the means were 3.4 versus 5.7).

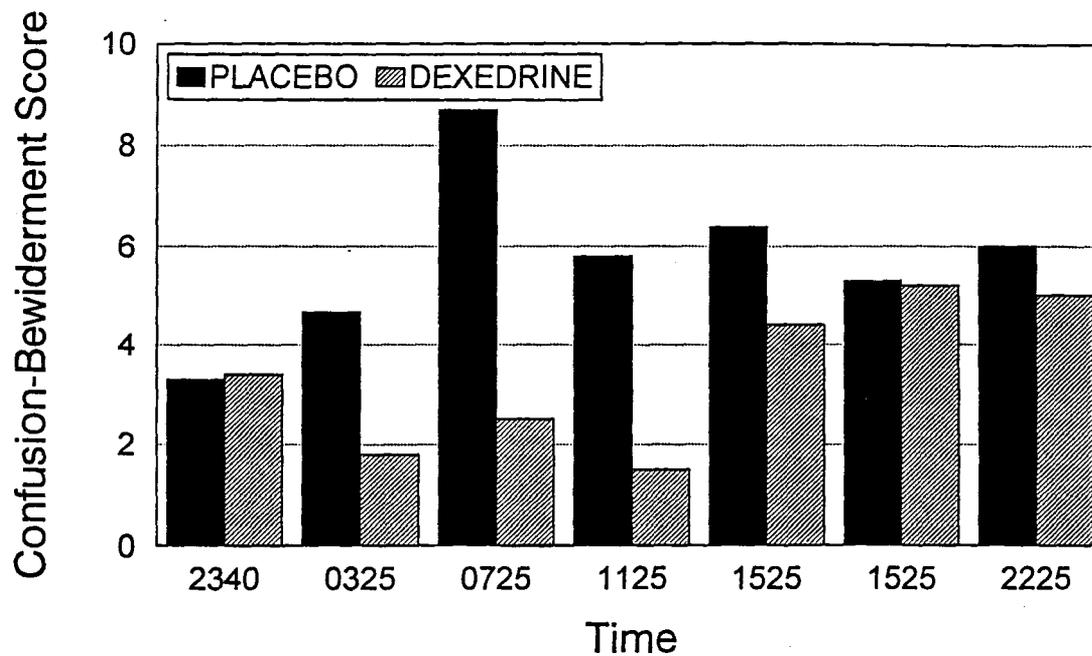


Figure 22. Effects of drug and time of day on POMS confusion-bewilderment ratings.

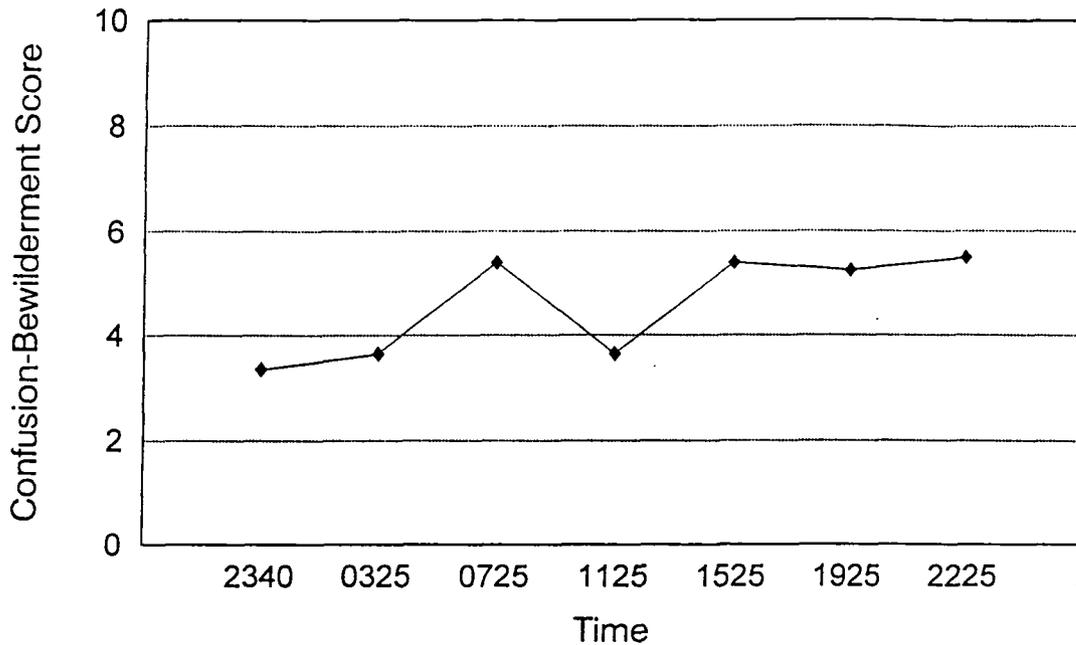


Figure 23. Effects of time of day on POMS confusion-bewilderment ratings.

### CFF

The analysis of CFF data was performed by averaging together the three ascending trials to yield one ascending frequency score per session and by averaging together the three descending trials to yield one descending frequency score per session. These averages were then analyzed in a 3-way repeated measures ANOVA in which the factors were drug (Dexedrine, placebo), session (0330, 0730, 1130, 1530, and 1930), and trial type (ascending, descending). The ANOVA indicated there was an interaction between drug and trial type ( $F(1,9)=10.62, p=.0099$ ) which subsequent analysis of simple effects indicated was due to a difference between the CFF frequency in the descending ( $p<.05$ ), but not the ascending trials (see figure 24). Within the descending trials, the mean CFF frequency under Dexedrine was higher than the one under placebo (40.84 Hz versus 39.42 Hz). In addition to this interaction, there was a main effect on the session factor ( $F(4,36)=4.59, p=.0028$ ). Contrasts revealed that the CFF frequency measured at 0330 was significantly lower ( $p<.05$ ) than ones collected at other times of the day. There was not an overall difference in the recorded CFF frequencies as a function of drug or trial type alone.

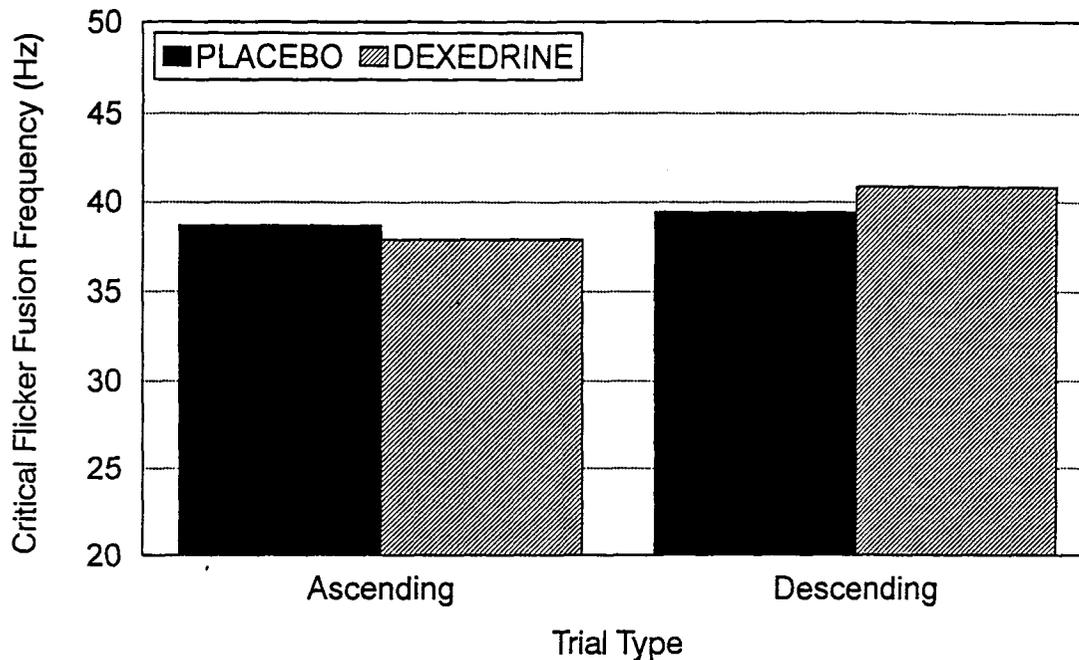


Figure 24. Effects of drug and trial type on critical flicker fusion frequency.

### MATB

The scores from the MATB tasks of monitoring, communications, resource management, and tracking were analyzed with 4 separate repeated-measures ANOVAs (one for each task) using BMDP 4V (Dixon et al., 1990). The factors were drug (Dexedrine and placebo) and session (0335, 0735, 1135, 1535, and 1935).

#### Monitoring

The monitoring task which required monitoring simulated gauges and warning lights was assessed in terms of response times to lights, response times to dial deviations, and time out errors for both. One subject's data were excluded due to an apparent misunderstanding of the instructions he was given. The ANOVA indicated there was a drug-by-session interaction on time outs for dials ( $F(4,32)=3.04, p=.0313$ ) which was due to more time out errors under placebo than Dexedrine at 0735, 1135, and 1535 ( $p<.05$ ) with no differences at 0335 or 1935 (see figure 25). In addition, there were session main effects on the mean reaction time for lights ( $F(4,32)=5.49, p=.0018$ ) and the standard deviation of reaction times for lights ( $F(4,32)=2.88, p=.0380$ ). As can be seen in figure 26, the mean reaction time for lights was slower at 0735 than it was at 0335, 1135, or 1935, and the standard deviation was higher at 0735 than it was at 1135 or 1935. In addition, the standard deviation was larger at 0335 than it was at 1935 ( $p<.05$ ).

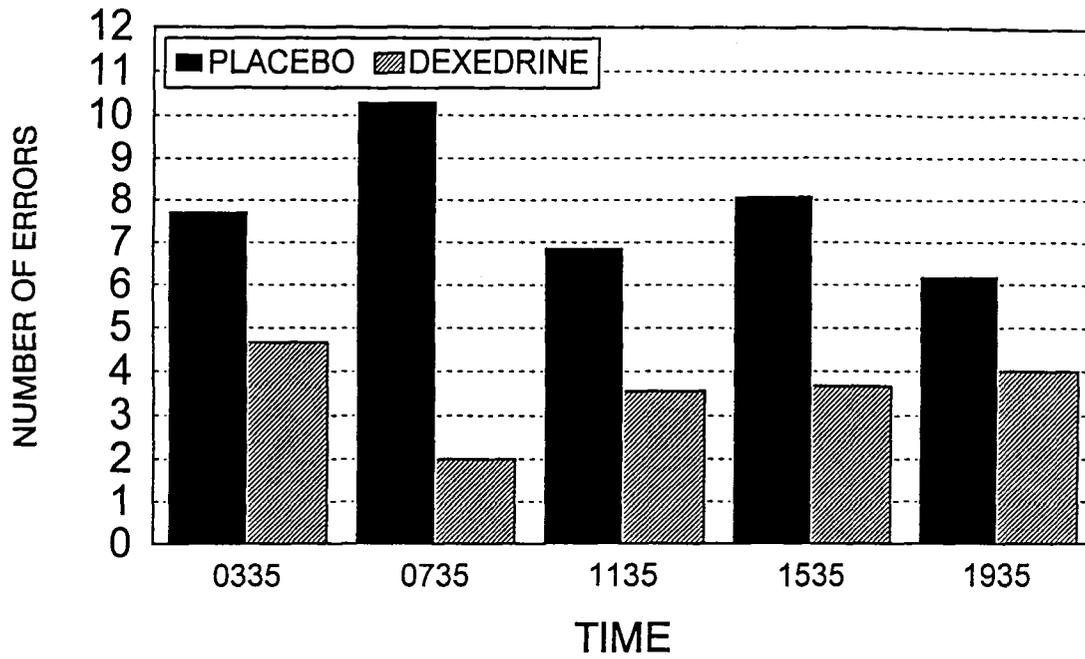


Figure 25. Effects of drug and time of day on errors in the monitoring task of the MATB.

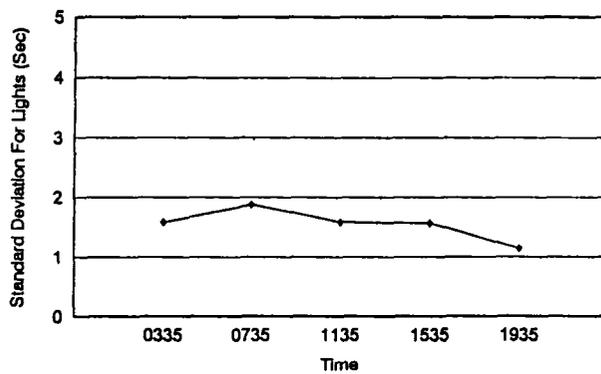
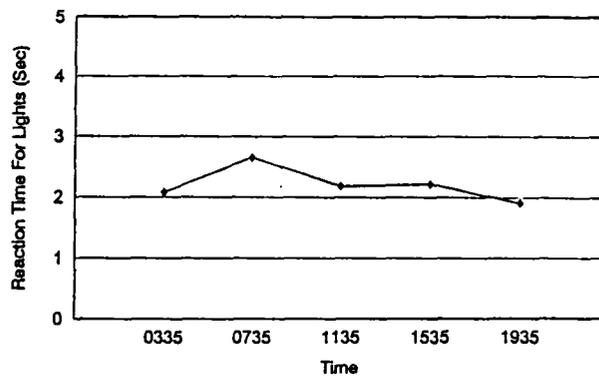


Figure 26. Effects of time of day on reaction times during the monitoring task.

There were drug main effects on the mean reaction time for lights ( $F(1,8)=13.31, p=.0065$ ), the mean reaction time for dials ( $F(1,8)=13.53, p=.0062$ ), the standard deviations for both lights ( $F(1,8)=5.82, p=.0424$ ) and dials ( $F(1,8)=7.31, p=.0269$ ), and the number of time out errors for lights ( $F(1,8)=6.43, p=.0048$ ) and dials ( $F(1,8)=14.94, p=.0048$ ). In each case, performance was slower, more variable, or inaccurate under placebo than under Dexedrine (see figure 27).

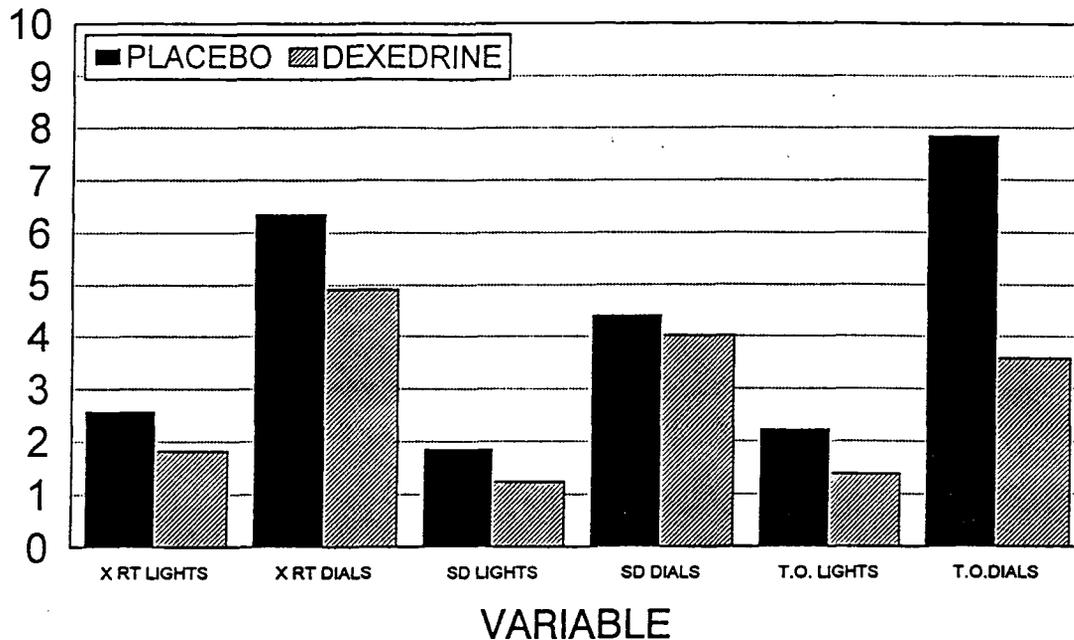


Figure 27. Effects of drug condition on performance on the monitoring task of the MATB.

### Communications

The communications task, which involved the subjects monitoring headphones and adjusting “radio frequencies” when instructed to do so, was analyzed in terms of the mean response time for correct responses, the standard deviation for correct responses, total number of errors (responding to the wrong call sign, changing to the wrong frequency, etc.), and number of false alarms, time outs, and incorrect responses. The analyses of these data indicated very few effects; however, there was an interaction between drug and session on the total number of errors ( $F(4,36)=4.75, p=.0035$ ) which was due to a marginal increase ( $p=.0665$ ) in the number of errors made under placebo as opposed to Dexedrine at 0735, but not at the other sessions (see figure 28).

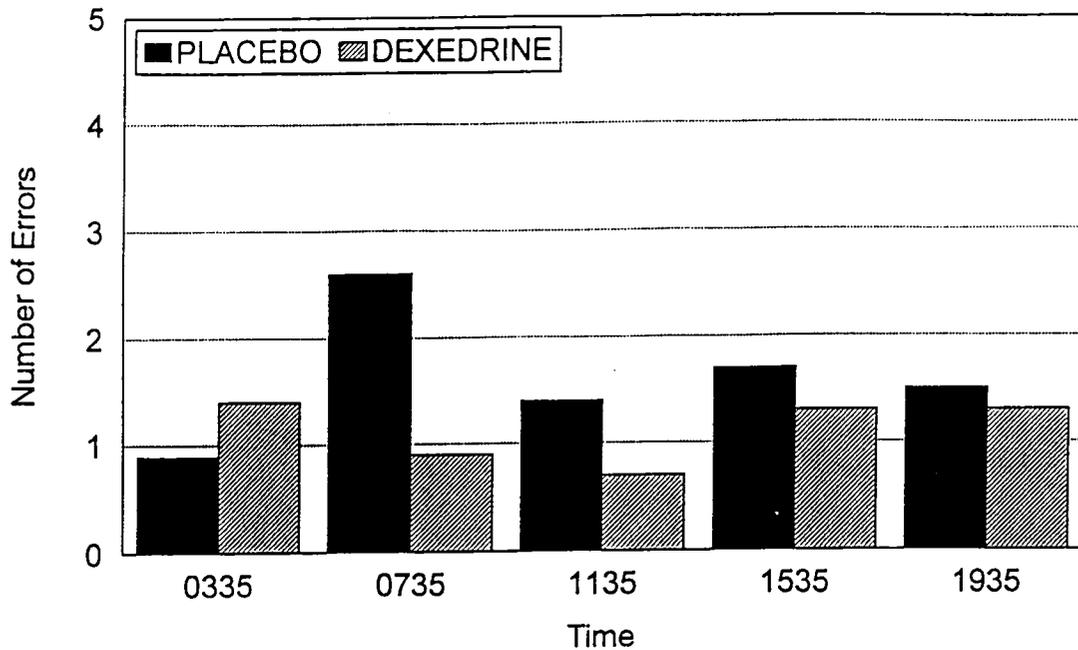


Figure 28. Effects of drug and time of day on errors during the communications task.

In addition to the interaction, there were session main effects on the mean reaction time for correct responses ( $F(4,36)=3.62, p=.0141$ ) and the total number of errors ( $F(4,36)=2.92, p=.0343$ ). The effect on mean reaction time was due to faster reactions at 1935 than at 0335 or 0735, and faster reactions at 1135 than at 0335 ( $p<.05$ ). The effect on total errors was because of fewer errors at 1135 than at 0735 or 1535 ( $p<.05$ ). These session effects are shown in figure 29.

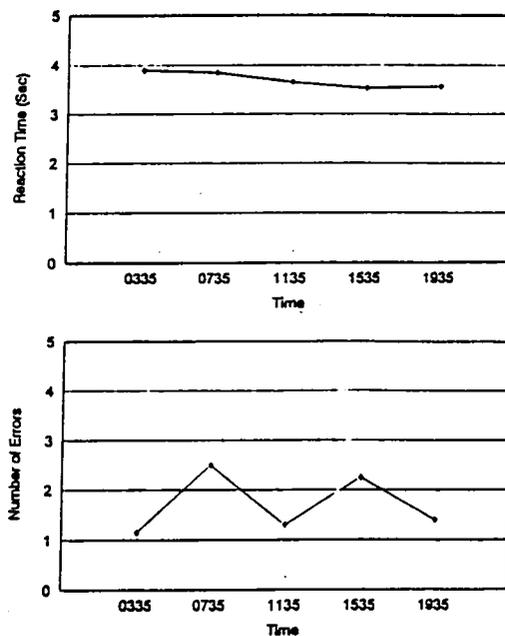


Figure 29. Effects of time of day on reaction times and errors on the communications task.

There were no significant drug main effects on this task. Of all of the variables analyzed, only the mean reaction time for correct responses was close to being better under Dexedrine than placebo, but the significance level was only .1061.

### Resource management

The resource management task, which required subjects to maintain the levels in two “fuel tanks” at 2500 units, was evaluated in terms of the mean absolute deviation of tanks one and two from 2500 units, the mean number of units maintained in tank one, and the mean number of units maintained in tank two. The ANOVA on this task indicated there were no main effects or interactions. The only effect approaching marginal improvement under Dexedrine was the number of fuel units maintained in tank one ( $p = .0639$ ).

### Tracking

Performance on the tracking task, which required subjects to maintain a target at the center of the tracking window through the use of a joystick, was evaluated in terms of the root mean square tracking error. The ANOVA revealed that tracking performance was significantly affected by the combination of drug and session ( $F(4,36) = 5.12, p = .0023$ ), the impact of session alone ( $F(4,36) = 32.13, p = .0062$ ), and the impact of drug alone ( $F(1,9) = 50.00, p = .0001$ ). The interaction was due to the fact that there was no difference between the Dexedrine and placebo conditions at 0335, but Dexedrine substantially improved performance relative to placebo at all of the remaining test times as can be seen in figure 30.

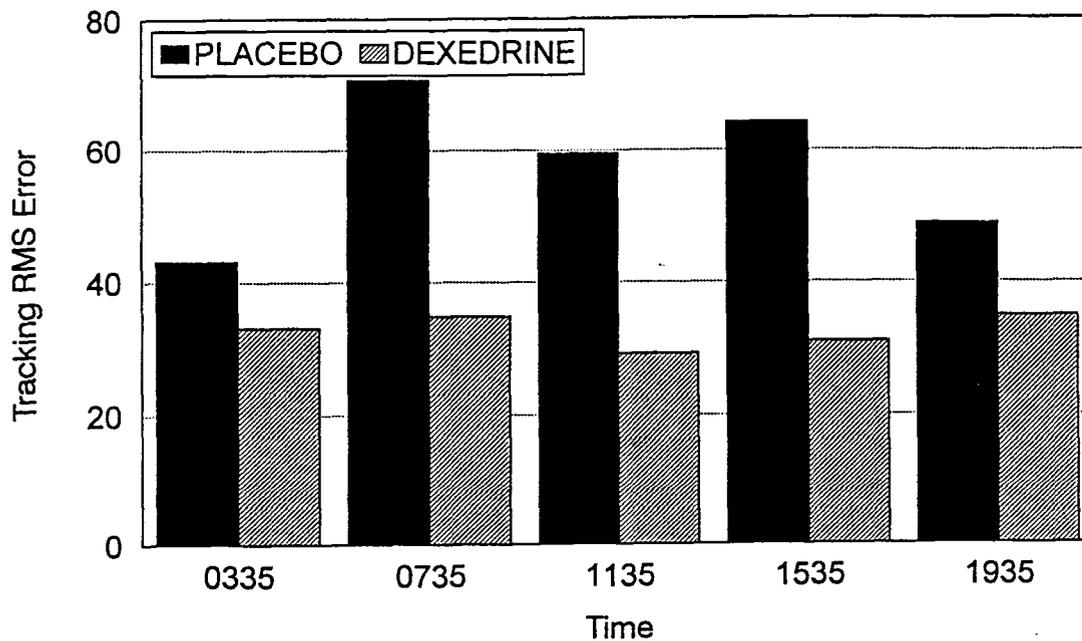


Figure 30. Effects of drug and time of day on tracking errors during the MATB.

The session main effect was attributable to a sharp increase in tracking errors at 0735 in comparison to those at 0335 and 1535, as well as a decline in errors from 0735 to 1135 ( $p < .05$ ). The drug main effect was due to better tracking accuracy under Dexedrine in comparison to placebo (the means were 32 versus 57, respectively).

### Vital Signs

The vital signs data were collected primarily for safety reasons as opposed to testing any hypothesis. However, these data were analyzed with BMDP 4V repeated measures ANOVA (Dixon et al., 1990). The two within-subjects factors were drug (Dexedrine and placebo) and time (2355, 0020, 0210, 0420, 0610, 0805, 1010, 1220, 1410, 1620, 1810, 2040, and 2220). Only the heart rate and blood pressure data will be reported since many of the oral temperature readings were confounded by the fact that subjects were eating or drinking in close proximity to the times at which vital signs were collected.

#### Heart rate

The ANOVA on the heart rate data indicated there was not a significant drug-by-time interaction, but there were significant main effects on the session ( $F(12,108)=6.55$ ,  $p < .0001$ ) and drug ( $F(1,9)=75.55$ ,  $p < .0001$ ) factors. The time effect was not pursued further because the precise nature of this effect would not contribute to understanding the impact of Dexedrine versus placebo and because numerous comparisons would be required to accomplish all pairwise contrasts. The drug main effect was due to a higher heart rate under Dexedrine than placebo (the means were 72.0 versus 67.4 beats per minute). The heart rates recorded throughout each deprivation period are presented in figure 31.

#### Systolic blood pressure

Analysis of the systolic blood pressure data showed there was no significant interaction, but there was a main effect on the session factor ( $F(12,108)=4.08$ ,  $p < .0001$ ) and the drug factor ( $F(1,9)=45.91$ ,  $p = .0001$ ). The session effect was not pursued further for the reasons cited earlier; however, the drug effect was due to higher overall blood pressure under Dexedrine than placebo (the means were 135.8 versus 127.7 mm Hg). These data are depicted in figure 32.

#### Diastolic blood pressure

The ANOVA on the diastolic blood pressure data indicated there was a significant drug-by-time interaction ( $F(12,108)=1.82$ ,  $p = .0532$ ) which analysis of simple effects revealed was attributable to higher blood pressures under Dexedrine versus placebo at 0210, 0420, 0801, 1010, 1220, 1620, and 2040 ( $p < .05$ ), but not at the other times (see figure 33). In addition, there was a main effect on the session factor ( $F(12,108)=5.12$ ,  $p < .0001$ ) which was not pursued further, and there was a main effect on the drug factor ( $F(1,9)=33.05$ ,  $p = .0003$ ) due to higher blood pressure under Dexedrine than placebo (the means were 77.3 and 71.5 mm Hg).

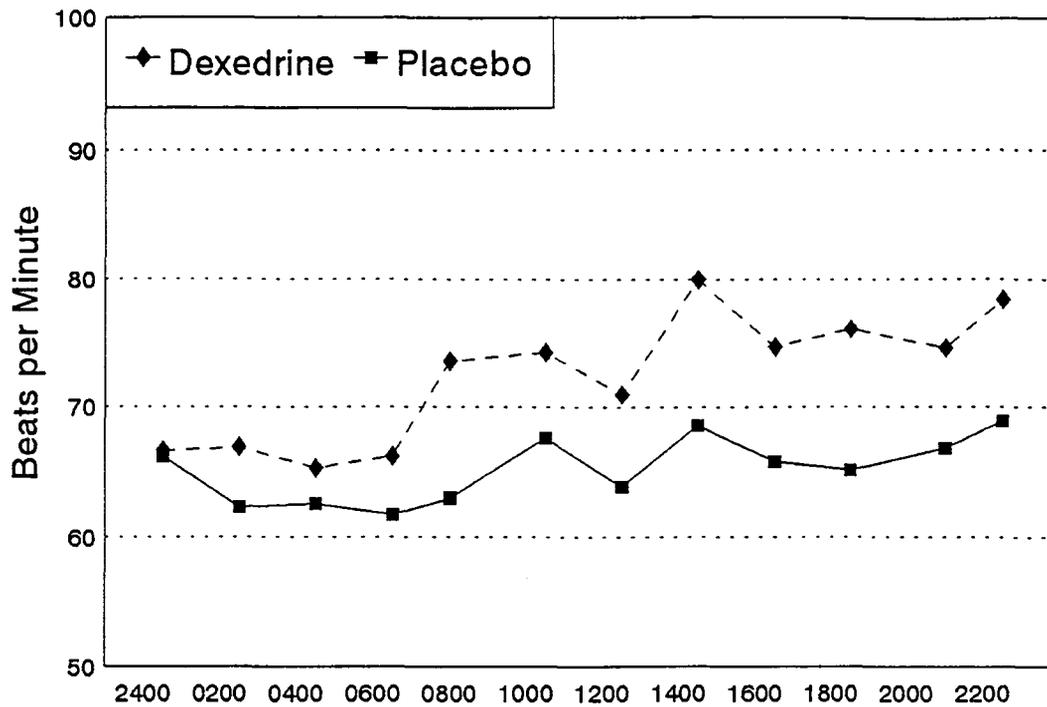


Figure 31. Effects of drug and time of day on heart rate.

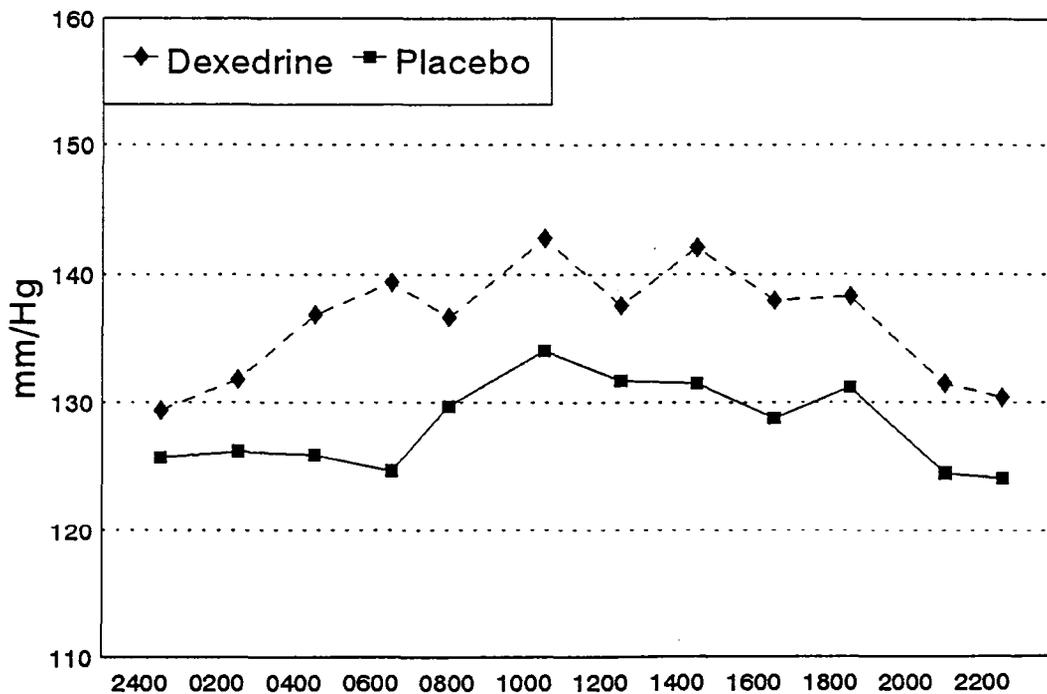


Figure 32. Effects of drug and time of day on systolic blood pressure.

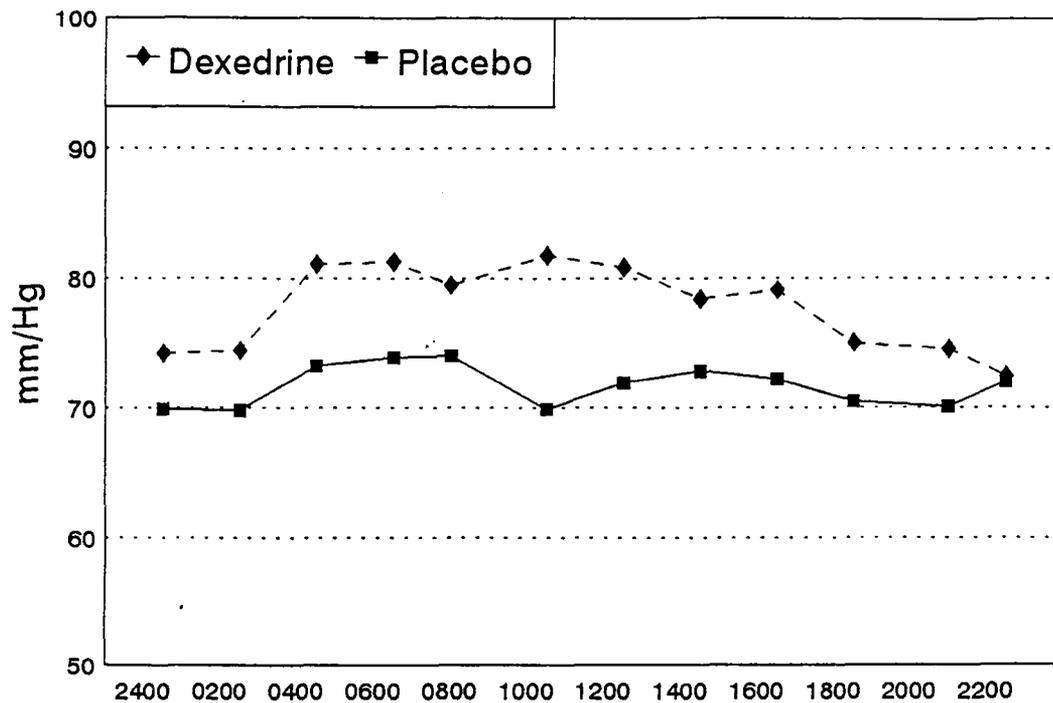


Figure 33. Effects of drug and time of day on diastolic blood pressure.

#### Polysomnography data

The latency to sleep onset, the percentage of time in each stage of sleep, the percentage of time subjects were awake after sleep onset (WASO), the latency to the first REM period, and the movement time during the sleep periods were each analyzed with a one-way analysis of variance with repeated measures over days (baseline, Dexedrine, and placebo). The data were transformed using the  $2 \cdot \arcsin$  square-root transformation to stabilize the variances prior to analysis. Significant main effects were followed with contrasts.

The results indicated a significant difference among the days for sleep onset ( $F(2,18)=12.68$ ,  $p=.0004$ ), percent stage 1 ( $F(2,18)=18.94$ ,  $p<.0001$ ), percent stage 2 ( $F(2,18)=7.58$ ,  $p=.0041$ ), percent stage 4 ( $F(2,18)=12.36$ ,  $p=.0004$ ), percent REM ( $F(2,18)=5.97$ ,  $p=.0103$ ), WASO ( $F(2,18)=7.24$ ,  $p=.0049$ ), movement time ( $F(2,18)=3.71$ ,  $p=.0449$ ), and REM latency ( $F(2,18)=4.79$ ,  $p=.0215$ ). Post hoc analyses of the days indicated a longer sleep onset (figure 34), more stage 1 and WASO, and less stage 4 sleep during baseline than after either Dexedrine or placebo. There also was more stage 2 sleep during baseline than following placebo, but not following Dexedrine (see figure 35). In addition, the analysis indicated a longer sleep onset, more stages 1 and 2 sleep, and less stage REM sleep following Dexedrine than following placebo. Analysis of time to the first REM period indicated a significantly longer latency following Dexedrine than following placebo (see figure 36).

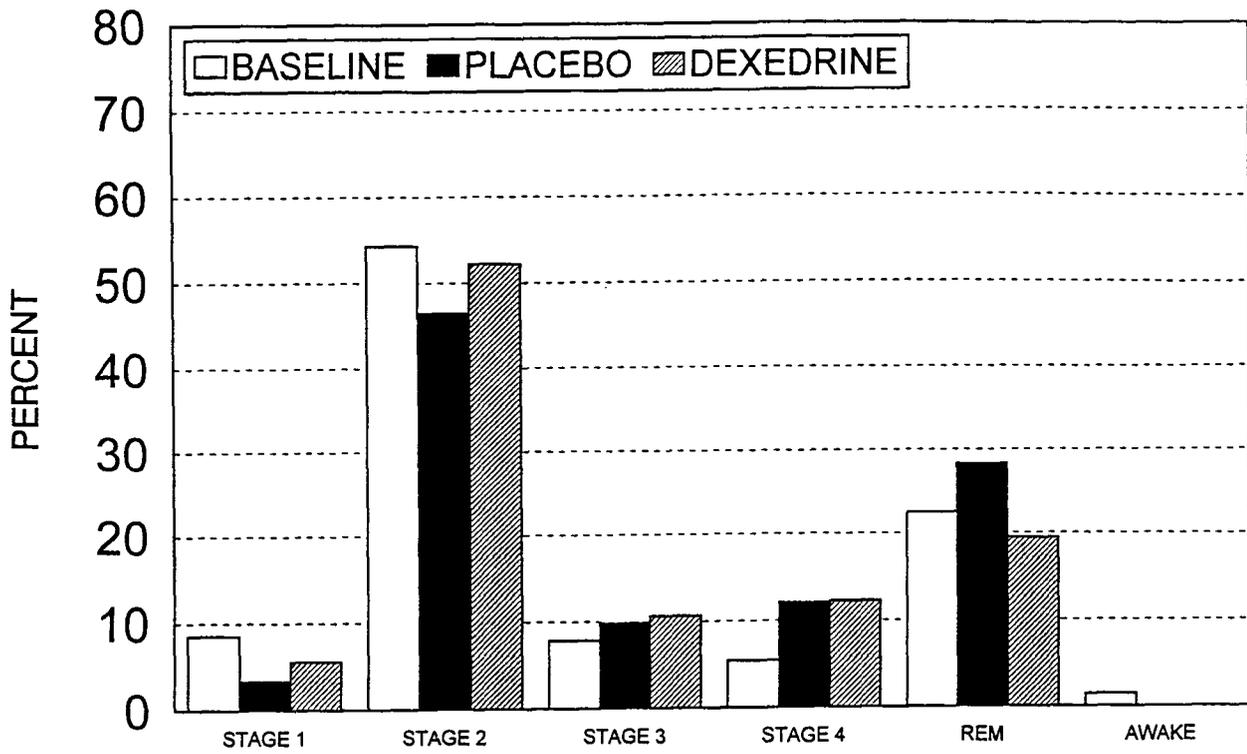


Figure 34. Effect of sleep night (and drug) on latency to sleep onset.

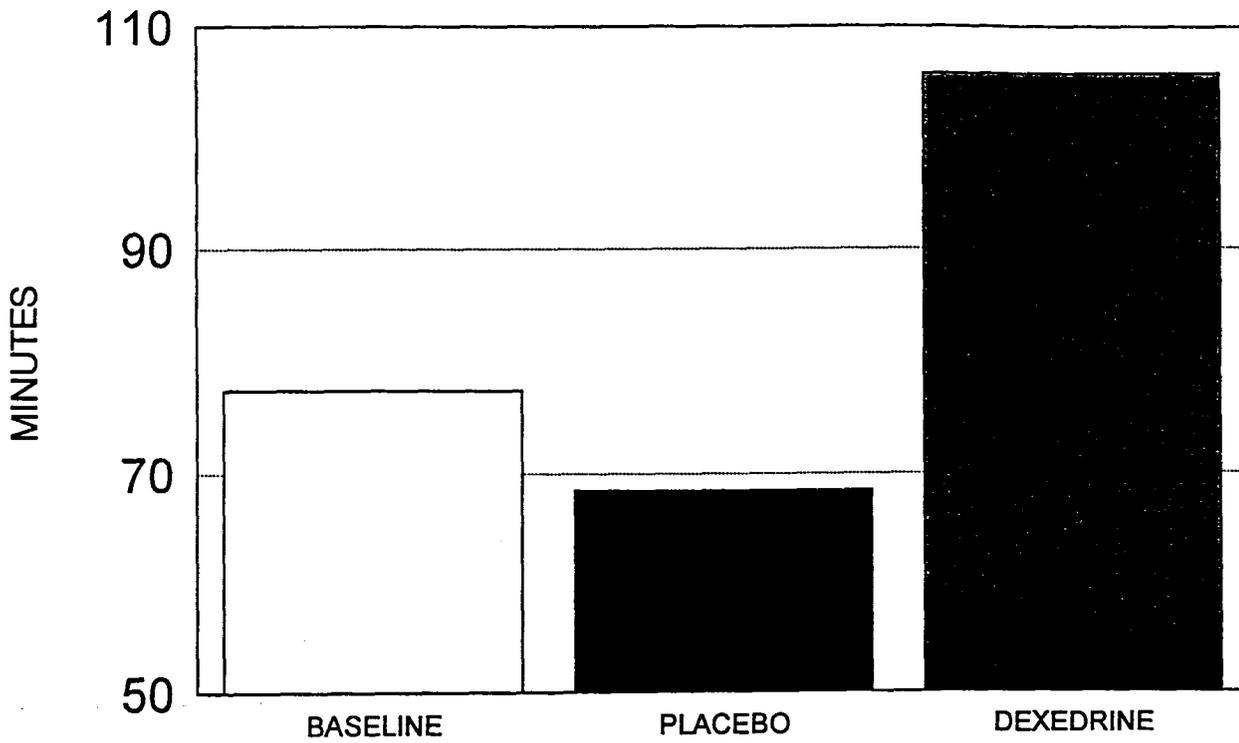


Figure 35. Effect of sleep night (and drug) on sleep architecture.

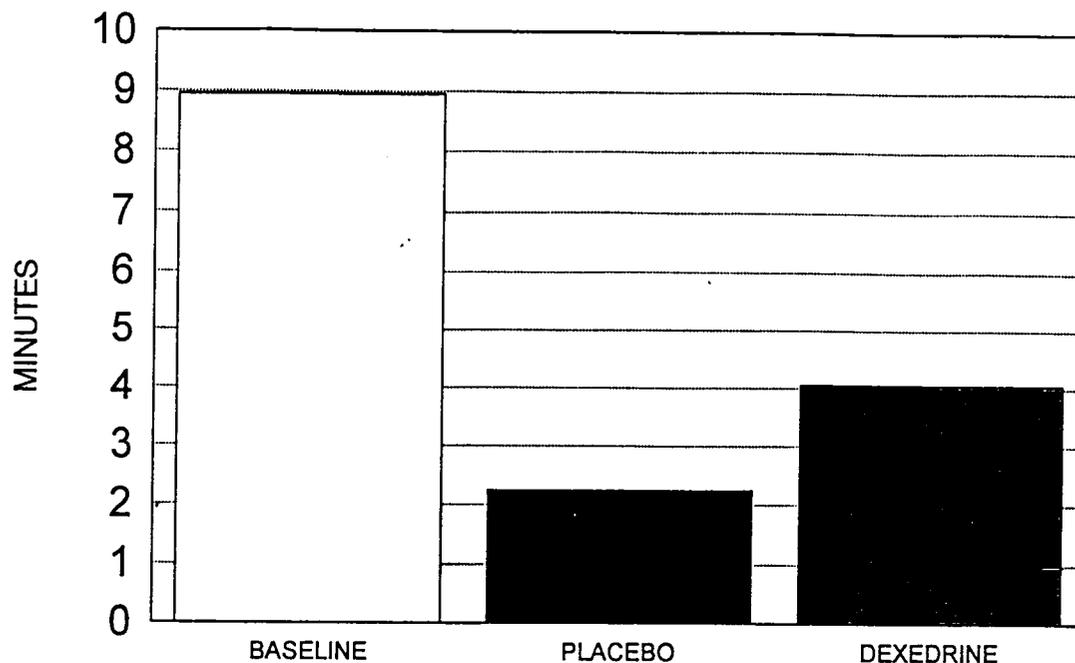


Figure 36. Effect of sleep night (and drug) on latency to the first REM period of sleep.

### Discussion

#### Flight performance

The analysis of helicopter pilot performance under actual in-flight conditions indicated that there were significant ( $p \leq .05$ ) reductions in RMS control errors under Dexedrine versus placebo on at least one measure in four of the seven maneuvers flown. In addition, there were marginally significant ( $p \leq .10$ ) reductions in control errors under Dexedrine versus placebo on two of the three remaining maneuvers. During the straight and level, both heading and airspeed control were affected; during the left standard rate turns, roll control tended to be affected; and during the climbs, differences were found on both heading and slip control. During the descent, there were drug effects on heading, airspeed, roll, and vertical speed control; on the left descending turn, there was a drug main effect on vertical speed control; and during the ILS approach, localizer tracking tended to be affected by drug administration. In each case, performance under Dexedrine was superior to performance under placebo.

Only the right standard rate turns showed no evidence of a drug main effect; however, there was a drug-by-iteration effect in which Dexedrine was found to substantially reduce vertical

speed control errors during the third turn (conducted without the AFCS) while there were no differences during the first or second turns (conducted with the AFCS). This is similar to the effect observed during the straight and levels, in which the largest benefit from Dexedrine compared to placebo was seen during the fourth straight and level which was conducted without the AFCS. In addition, there was a marginally-significant ( $p < .07$ ) improvement in airspeed control under Dexedrine versus placebo during the second left standard rate turn (conducted without the AFCS), but not during the first left standard rate turn (conducted with the AFCS). The fact that maneuvers flown without the aid of the AFCS were most sensitive to fatigue effects (and Dexedrine's mitigation of these effects) is consistent with the results from an earlier simulator study (Caldwell et al., 1994). The increased workload brought about by the removal of this computerized flight-path stabilization system no doubt increases the difficulty pilots have compensating for performance decrements produced by sleep deprivation, and this increases the degree of separation between the Dexedrine and placebo conditions.

Drug-by-session interactions were observed only in the left descending turn and the ILS approach. In the left descending turn, roll control errors were significantly smaller under Dexedrine than placebo at the 0900 flight, but there were no differences elsewhere. A similar effect was seen in vertical speed control on this same maneuver where Dexedrine reduced control errors relative to placebo both at 0500 and 0900. On the ILS approach, an unexpected reversal of the Dexedrine-placebo relationship was seen on slip control in that errors were actually larger under Dexedrine than placebo at 0500. However, on this same maneuver, there was a marginal ( $p = .09$ ) effect on glideslope tracking which indicated that Dexedrine tended to be better than placebo at 1300, but not elsewhere. Although the findings with slip control during the ILS are difficult to explain, the findings with roll and vertical speed control during the left descending turn are consistent with past results (Caldwell et al., 1994; Caldwell et al., 1995) in which the greatest benefit from Dexedrine was observed at the 0500 and 0900 flights. This is because Dexedrine is most beneficial when fatigue is greatest, as is the case from about 0300 to 1100.

It is noteworthy that of the 18 drug-related effects on flight performance, all were in the predicted direction (Dexedrine better than placebo) with the exception of only 2 effects. The fact that Dexedrine's positive effects were consistent across a variety of maneuvers, and the fact that the results from this in-flight study are in agreement with those from two earlier simulator studies, lends substantial support to our original conclusions that Dexedrine is a feasible countermeasure for fatigue in aviation continuous operations scenarios.

#### Electroencephalographic activity

The results from the resting eyes-open/eyes-closed EEGs indicated that there were no drug-related effects on delta activity as expected based on the results of earlier research (Caldwell et al., 1994; Caldwell et al., 1995), although there were non-significant trends towards more delta under placebo than Dexedrine. However, there were substantial drug-related changes in theta power at several electrode sites. Specifically, there were elevations in theta activity under the placebo condition at all three central recording sites and one parietal site. These findings are

consistent with results from earlier simulator studies on Dexedrine versus placebo, and they are generally consistent with the findings of other investigators (Pigeau, Heslegrave and Angus, 1987; Comperatore et al., 1993; Lorenzo et al., 1995) who have reported increased slow-wave EEG activity as a function of sleep deprivation.

In addition to the increases in slow-wave theta activity under placebo, there were decreases in faster alpha activity under placebo compared to Dexedrine. This effect was not surprising considering that the onset of sleep is characterized by a reduction in alpha activity as well as an increase in slow, rolling eye movements. The fact that alpha activity was maintained at a higher level under Dexedrine than placebo simply shows that subjects were less likely to fall asleep under the influence of Dexedrine. In fact, the significant interactions between drug and eyes (i.e., eyes open/eyes closed) indicated this difference in alpha activity was most noticeable when subjects closed their eyes. The combined impact of sleep loss and the placing of subjects in a position that was more conducive to sleep (eyes closed), promoted the tendency for subjects to doze off for brief intervals. Other evidence that these brief episodes of sleep did in fact occur was seen in the drug-by-eyes interactions found in the theta band where there was more theta under placebo versus Dexedrine with eyes closed than was the case with eyes open.

These EEG effects indicate that subjects were significantly more alert after receiving Dexedrine than placebo. Such findings are consistent with the performance data because the overall improvements in alertness under Dexedrine no doubt contributed to improvements in flight performance discussed earlier. Conversely, the reductions in alertness under placebo placed subjects at greater risk for brief lapses into sleep during which performance would have been less precise.

#### Desktop flight simulator

The analysis of both speed and accuracy data from the Microsoft desktop flight simulator indicated there were no significant main effects or interactions on this task. These results are not consistent with those of Caldwell et al. (1994) in which desktop flight simulator performance was found to be better under Dexedrine than placebo especially toward the middle of the day. However, the present results are consistent with those from a later study (Caldwell et al., 1995), in which no differences were found as a function of whether female pilots were administered Dexedrine or placebo. Reasons for these discrepancies are unclear; however, it may be that this test is affected more than some of the others by differences in the amount of training required to reach asymptotic levels. Also, it may be that the impact of missed "gates" on the overall score contributes enough error variance so as to require very large experimental effects before statistical significance is attained. In the past, it has been possible to retest subjects who missed a gate during the desktop flight simulator session; however, time constraints prevented retesting in the present investigation. Perhaps these factors resulted in the absence of any discernable drug-related trends in this data set.

## POMS

The POMS data indicated changes in subjective mood ratings consistent with what was expected as a function of sleep deprivation. Specifically, there were significant drug-by-session interactions on depression-dejection, vigor-activity, fatigue-inertia, and confusion-bewilderment. Although the effect on depression-dejection was due to an improvement under Dexedrine relative to placebo at only one session (0725), the other scales revealed substantial Dexedrine-related improvements at 0325, 0725, and 1125. Also, on the vigor-activity and fatigue-inertia scales, there were positive Dexedrine effects as late as 1925 and 2225, respectively. In general, these results support the findings of Newhouse et al. (1989) who found that dextroamphetamine (relative to placebo) improved vigor and fatigue ratings during sleep deprivation, and those of Pigeau et al. (1995) who reported that positive mood, sleepiness, and fatigue ratings were improved under dextroamphetamine versus placebo during simulated sustained operations. In addition, the interactions between mood scores and time of day support the earlier studies by Caldwell et al. (1994) and Caldwell et al. (1995) in which it was determined that the largest differences in mood between Dexedrine and placebo occurred at the times of day when fatigue effects were greatest (i.e., from about 0300 until about 1100). Behavioral observations of the subjects indicated they were suffering most from the effects of sleep loss in the early portion of the day, whereas around noon, they appeared to “get their second wind.” These subjective impressions combined with the POMS ratings coincide especially with the flight performance results on the left descending turn which showed the largest disparity in control accuracy under Dexedrine versus placebo at the 0500 and 0900 flights.

## CFF

Critical fusion frequency is one measure of cortical activation used in drug research. For instance, in investigations of the stimulant Modafinil, it has been reported that CFF decreases with reductions in cortical activation caused by sleep deprivation (Bensimon et al., 1991), and CFF increases in response to stimulant administration (Saletu et al., 1986). Increases in CFF have been accompanied by improvements in attention, reaction time, and affectivity (Saletu et al., 1986). In the present investigation, overall increases in CFF were found in the descending, but not the ascending, trial types. This is consistent with at least one study (Aiba, 1959, reviewed in Smith and Misiak, 1976) which suggested that descending trials may be more sensitive to drug effects than ascending trials. The more important finding from the present investigation was that CFF increased under Dexedrine compared to placebo, consistent with expectations based on earlier research (reviewed in Smith and Misiak, 1976). This suggests that central nervous system activation was improved by Dexedrine, and this interpretation is supported by the fact that improvements were observed in both the flight and the mood data under Dexedrine versus placebo.

## MATB

Performance on the simulated aviation tasks of monitoring lights and dials, performing radio communications tasks, managing fuel, and tracking targets revealed a variety of effects which indicated Dexedrine was effective in sustaining aviator performance. Subjects in this investigation were faster at responding to the onset of warning lights and the presence of dial deviations, slightly better at completing the communications task, and more accurate in tracking a target under Dexedrine than placebo. These results are supportive of those found by Hartmann, Orzack, and Branconnier (1977) that subjects made fewer errors of omission after dextroamphetamine versus placebo on a vigilance task; results by Higgins et al. (1975) that subjects responded better to warning lights under dextroamphetamine than placebo; and results by Seashore and Ivey (1953) that tracking skill was improved by amphetamine in comparison to placebo. In addition, drug-by-session interactions on time out errors for dials, total errors for communications, and RMS errors on the tracking task indicated that many of the largest differences between Dexedrine and placebo occurred in the morning hours. There were more time out errors for dials under placebo than Dexedrine at 0735, 1135, and 1535; more total communications errors under placebo than Dexedrine at 0735; and greater tracking errors under placebo versus Dexedrine at 0735. These data agree with findings from portions of the flight and POMS data which indicated the greatest benefit from Dexedrine occurred during the times of day when fatigue levels were most severe. It is noteworthy that the MATB task which required the most vigilance (tracking) was one of the tasks most obviously affected by fatigue effects--a finding consistent with the notion that sleep deprivation affects vigilance-based tasks more than others (Dinges, 1995).

## Vital signs

The heart rate and blood pressure data showed drug-related effects which were generally consistent with what was expected based on earlier research (Caldwell, in press; Newhouse et al., 1989). There were overall increases in heart rate, systolic blood pressure, and diastolic blood pressure under Dexedrine in comparison to placebo. Examination of the means of each of these measures showed a 5 beat-per-minute increase in heart rate, an 8 mm Hg increase in systolic blood pressure, and a 6 mm Hg increase in diastolic blood pressure under Dexedrine relative to placebo. None of these elevations were clinically significant.

One difference between the results of this in-flight study and the earlier simulator studies (Caldwell et al., 1994; Caldwell et al., 1995) was that no drug-by-time interaction on the heart rates or the systolic blood pressures were found. An examination of the means on the heart-rate data suggested a tendency for there to have been larger differences in heart rates under Dexedrine versus placebo from 0800 until the end of the day in comparison to the those recorded prior to 0800--an effect which tends to be consistent with the earlier simulator results. However, with regard to the systolic blood pressures, it appeared that the systolic pressure under Dexedrine tended to increase around 0400 and then remain higher than the systolic pressure under placebo for the remainder of the day. This finding is not consistent with earlier results which showed a

clear Dexedrine-related increase in systolic blood pressure towards the middle of the day, but not at either the beginning or the end. Perhaps the fact that there were more tobacco users in the present research than in the earlier studies, or that there was more physical activity in this investigation compared to earlier ones, accounts for the difference; however, these explanations are purely speculative at this point.

### Polysomnography

Findings concerning the sleep quality of subjects under Dexedrine versus placebo in this study were similar to those from the earlier simulator studies (Caldwell, Caldwell, and Crowley, 1996). Of particular interest was the fact that sleep latency was prolonged, the amount of REM sleep was reduced, the latency to the first REM period was lengthened, and the percentages of stages 1 and 2 sleep were elevated on the night after Dexedrine was administered as compared to the night after placebo was administered. This indicates that sleep after Dexedrine was slightly less restful than sleep after placebo regardless of the fact that the last drug dose was given 15 hours prior to bedtime. Dexedrine has a half-life of approximately 10.25 hours. Thus, it is important that when Dexedrine is given to aviators for the maintenance of alertness during sustained operations, efforts are made to ensure that the drug is discontinued early enough to avoid interference with subsequent recuperative sleep periods.

### Conclusions

This investigation was the first controlled, in-flight study of the efficacy of Dexedrine for sustaining the performance of sleep-deprived aviators. It was performed to systematically replicate the methodology employed in previous simulator studies (Caldwell, Caldwell, and Crowley, 1996), and to determine whether the results can be generalized to the actual flight environment. Although the present investigation used only UH-60 pilots as subjects, the results should be applicable to the larger population of all types of aviators because the cognitive and psychomotor demands of flying a UH-60 helicopter are similar to the demands associated with flying other aircraft. In addition, past research suggests that pilots as a group (regardless of primary aircraft flown) tend to have similar psychological characteristics (Caldwell et al., 1993).

The results of this in-flight evaluation were consistent with the earlier studies in that Dexedrine effectively maintained several aspects of flight performance, cognitive performance, psychomotor skill, positive psychological mood, and central nervous system arousal of sleep deprived pilots better than placebo. Although Dexedrine did not exert a significant impact on every variable investigated, there were sufficient positive effects consistent with those found in earlier investigations to conclude that Dexedrine is efficacious for the short-term maintenance of aviator performance in sustained operations.

These results support previous suggestions that dextroamphetamine should be considered a viable countermeasure for fatigue and sleep deprivation in operational environments (Caldwell,

Caldwell, and Crowley, 1996; Cornum, Caldwell, and Cornum, in press; Cornum, Cornum, and Storm, 1996; Emonson and Vanderbeek, 1995; and Senechal, 1988). Although Dexedrine produced general cardiovascular stimulation and slight impairments in sleep quality, these negative effects appear to be inconsequential compared to the significant positive improvements in flight performance, mood, and alertness associated with this medication. Dexedrine, administered prophylactically, is particularly beneficial for preventing the dangerous reductions in aviator performance and alertness that are most evident between 0300 and 1000 in the morning. In situations where sleep deprivation is unavoidable, Dexedrine could make the difference between life and death if it is administered properly.

Future research should address the issue of whether or not longer-term use of dextroamphetamine is a viable option for personnel who may be sleep deprived for periods of 3-4 days. Unfortunately, studies on this point have not yet been conducted. It may be that the short-term benefits from Dexedrine disappear after 1-2 days because of sleep-pressure, drug tolerance, or physiological stresses. However, until these factors can be investigated, it may be concluded that Dexedrine is a good countermeasure for sleep deprivation in operations that require up to 40 hours of continuous wakefulness. Caution should be exercised when using this medication for more prolonged periods.

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Appendix

Manufacturer's list

Cadwell Laboratories  
909 North Kellogg Street  
Kennewick, WA 99336

CH Products  
970 Park Center Drive  
Vista, CA 92083

Coulbourn Instruments, Incorporated  
Box 2551  
Lehigh Valley, PA 18001

Critikon  
4110-T George Road  
Tampa, FL 33614

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

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

Grass Instrument Company  
101 Old Colony Avenue  
Quincy, MA 02169

IVAC Corporation  
10300 Campus Point Drive  
San Diego, CA 92121

Lafayette Instrument Company  
Lafayette, IN 47903

Marquette  
8200 West Tower Avenue  
Milwaukee, WI 53223

MicroSoft  
1 Microsoft Way  
Redmond, WA 98052

Nihon Kohden  
17112 Armstrong Avenue  
Irvine, CA 92714

Paravant  
7800 Technology Drive  
Melbourne, FL 32904

Perkin Elmer Corporation  
Marn Avenue  
Norwalk, CT 06886

SensorMedics  
22705 Savi Ranch Parkway  
Yorba Linda, CA 92687