Dextroamphetamine and Modafinil are Effective Countermeasures for Fatigue in the Operational Environment

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ABSTRACT

Fatigue has been identified as an important operational problem in both military and civilian aviation. Requirements for extended duty periods, inconsistent work/rest schedules, multiple-time-zone operations, and night flights combine to potentially degrade performance and alertness in the cockpit. Duty-time limitations traditionally have been relied upon to manage aircrew fatigue; but problems persist as evidenced by the fact that significant fatigue-related mishaps continue to occur. Because of this, it is worthwhile to consider the limited use of alternative strategies such as stimulants. The data from five placebo-controlled studies (four with dextroamphetamine and one with modafinil) were combined to examine the overall efficacy of stimulants for preserving flight performance, physiological alertness, and subjective vigilance in sleep-deprived pilots. Statistically-significant ($p<.05$) drug main effects and drug-by-time interactions revealed that both compounds maintained flight performance across six maneuvers, attenuated deprivation-related increases in slow-wave electroencephalogram (EEG) activity, and preserved subjective ratings of psychological vigor throughout 34-39 hours of continuous wakefulness, whereas substantial difficulties were observed under placebo. Dextroamphetamine and modafinil are effective for sustaining aviator alertness and performance (although, some potentially dose-related adverse effects were observed with modafinil). While it may be ill-advised to rely upon the long-term use of these or other pharmacological strategies as the sole remedy for fatigue in aviation, stimulants can be counted upon to temporarily mitigate the deleterious effects of fatigue during operations in which no other countermeasures are feasible.

1.0 INTRODUCTION

Pilot fatigue is a significant problem in modern aviation operations, largely because of the unpredictable work hours, long duty periods, circadian disruptions, and insufficient sleep that are commonplace in both civilian and military flight operations (1, 2). The full impact of fatigue is often underappreciated, but many of its deleterious effects have long been known. Lindberg recognized the detrimental consequences of long duty hours (and long periods of wakefulness) on flight performance back in the 1920's, and scientists began to appreciate the negative impact of rapid time-zone transitions in the early 1930's (3).

As science has progressed, it has become increasingly clear that aircrew fatigue is primarily a function of scheduling and workload (2), and that of these two factors, scheduling is the more important issue. In fact, the

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fatigue associated with crew duty scheduling has been implicated in air mishaps. A National Transportation Safety Board (NTSB) study of major accidents in domestic air carriers from 1978 through 1990 in part concluded that ". . . Crews comprising captains and first officers whose time since awakening was above the median for their crew position made more errors overall, and significantly more procedural and tactical decision errors" (p. 75) (4). Kirsh (5) estimated that fatigue may be involved in 4-7% of U.S. civil aviation mishaps, and statistics from the Air Force Safety Center blame fatigue, at least in part, for 7.8% of Air Force Class A accidents and incidents (6).

1.1 An Overview of Factors Contributing to Aircrew Fatigue

An examination of the schedules worked by modern military and commercial pilots reveals that they and their crews are routinely exposed to duty cycles that 1) challenge innate biological rhythms, 2) acutely and chronically truncate sleep, and 3) require prolonged work periods. All of these are important components of the fatigue factor.

1.1.1 Circadian Factors

Akerstedt (7) points out that when work hours are in conflict with human biological programming, alertness impairments often result. There is a known biological propensity towards sleepiness and inactivity at night, whereas arousal and heightened activation more naturally occur during the day. Studies on pilots have shown that attention lapses and flight-control deviations are more frequent and more severe when flights overlap the subjective nighttimes of crewmembers (8). Lyman and Orlady (9) found that the majority of fatigue-related flight incidents in one sample of NASA's Aviation Safety Reports System occurred between midnight and 0600 in the morning. Furthermore, Klein et al. (10) reported that simulator flight performance at 0400 in the morning degraded to 75-100% below what was typical at 1500 in the afternoon. Thus, the impact of circadian factors on pilots engaged in what might be considered routine shift work is clear. In addition, it has been shown that circadian misalignment associated with rapid transmeridian travel exerts a negative effect on alertness and performance during duty periods, as well as disrupting sleep during rest times. Eastward flights are generally more problematic than westward flights (11). In fact, it has been established that circadian resynchronization rates are 50% slower after eastbound than after westbound travel across multiple time zones, and this in-and-of-itself can interfere with recuperative sleep (12, 13). Following eastward transitions, sleep patterns are more variable and fragmented (14). Following westward transitions, sleep problems are less severe (15), but reduced sleep efficiency and duration have nonetheless been reported despite the fact that the longer biological day makes the layover sleep easier to initiate (16).

1.1.2 Shortened Sleep Periods

Military pilots suffer sleep disturbances or truncated sleep because of the high demands associated with operational missions. Paul, Pigeau, and Weinberg (17) discovered that during the days prior to some re-supply missions from Canada to the former Yugoslavia, the sleep of Canadian CC-130 pilots steadily decreased from 8.7 hours per day to 6.5 hours per day before departure. Boll et al. (18) indicated that many C-141 pilots slept only 6.7 hours per day during Desert Storm or 6.4 hours per day during Desert Shield. Neville et al. (1) reported that during the final week of Desert Storm, there were severe sleep deficits in at least one sample of C-141 crews. Despite regulations requiring a minimum crew rest period of 12 hours (19), some pilots obtained no sleep at all during entire 24-hour cycles. Bisson, Lyons, and Hatsel (20) found that C-5 crews during Operation Desert Shield often reported for duty with less than 4 hours of sleep in the previous 12-16 hours.

1.1.3 Lengthy Duty Periods

Long duty cycles and consequent lengthy periods of continuous wakefulness are difficulties frequently faced by civilian aviators, and to a larger extent, their military counterparts. In sustained military operations, duty days sometimes extend beyond 20 hours (20) and the mission itself can be over 35 hours in duration (21). In the long-haul civilian sector, Samel, Wegmann, & Vejvoda (22) discovered that pilots were awake for as long as 22 continuous hours on outbound legs. Such prolonged duty periods are disconcerting in light of the fact that Goode (23) found that the probability of a commercial airline accident increases significantly as a function of time on duty. Although only 10% of pilot duty hours were found to exceed 10 hours in duration, 20% of all U.S. commercial aviation mishaps appear to occur at the 10th hour and beyond. Only 1% of duty time exceeds 13 hours or more, but 5% of the mishaps occur within this time frame.

1.2 Fatigue Countermeasures

Clearly, circadian disruptions, acute or cumulative sleep deprivation, and prolonged periods of continuous wakefulness contribute substantially to pilot fatigue, and increased fatigue has been associated with an increased risk of incidents and accidents. For these reasons, effective fatigue countermeasures are necessary to preserve aviator performance and safety in circumstances that are often less than optimal. Such countermeasures can be classified into two large categories: 1) Non-drug, and 2) Drug.

1.2.1 Non-Drug Strategies

Generally speaking, non-drug strategies should be attempted before resorting to medications because non-drug strategies tend to place less of a burden on medical resources that are already taxed, and in the long run, non-drug remedies tend to pose a lower risk of complications (i.e., drug dependence or abuse). Included in this category are strategies such as on-board, out-of-cockpit sleep episodes (24), cockpit naps (25), work/rest schedules that have been optimized with performance-prediction tools (26, 27), controlled activity breaks (28), properly-timed bright light exposure (29,30,31), and postural changes (32).

1.2.2 Drug Strategies

However, when such non-pharmacological approaches become ineffective or impractical, medication-based strategies should be considered, particularly in the military context. Within the domain of drug-based counter-fatigue interventions, there are two approaches. The first, which will not be discussed in detail here, is to *utilize hypnotic compounds* such as temazepam (33), zolpidem (34), or zaleplon (35) to maximize the advantages that crews can take to gain sleep in situations where sleep opportunities are available, but are compromised by circadian factors or extremely stressful or uncomfortable environments. The second is to *utilize alertness-enhancing compounds* such as caffeine (36), dextroamphetamine (37), or modafinil (38, 39) to sustain sleep-deprived crews until they can gain suitable amounts of recovery sleep. This later strategy is the subject of the present report.

1.2.2.1 Caffeine

Although caffeine is a known stimulant, it will not be further discussed here since it already is an acceptable and freely-available product in widespread use, and since it generally does not necessitate medical oversight. However, dextroamphetamine and modafinil, the often more contentious alertness enhancing medications, will receive the primary emphasis.

1.2.2.2 Amphetamines

Amphetamines have been on the market in the U.S. since 1937 (40), and U.S. forces are authorized to utilize dextroamphetamine in combat aviation operations. As will be noted in detail shortly, multiple 10-mg doses of dextroamphetamine can sustain the performance of pilots throughout 40 hours of continuous wakefulness (41, 42, 43), and even throughout 64 hours without sleep (44). Field experience with this compound has generally been positive (45), with little or no indication of increases in risk-taking behaviors or overestimation of performance capabilities (44, 46, 47). However, since amphetamines are known to be drugs of abuse, there is interest in providing potential alternatives.

1.2.2.3 Modafinil

Modafinil is a newer alertness-enhancing compound that is efficacious for sustaining performance during periods of total sleep loss (48). Testing in aviation-relevant (and other military) contexts is quite limited, but a helicopter-pilot study (with 600 mg modafinil given in three divided 200 mg doses) indicated modafinil was capable of sustaining simulator flight performance at near rested levels despite over 30 hours of sleep loss (38). Also, a fighter-pilot study (with 300 mg modafinil given in three divided 100-mg doses) indicated that modafinil effectively attenuated fatigue decrements in simulator flight performance, mood, and cognition across a similarly lengthy period (39).

These results demonstrate there is a role for dextroamphetamine and modafinil in select aviation operations because they have noteworthy alertness-enhancing properties that can enhance the safety of aircrews under situations in which extreme operational fatigue is simply unavoidable. To clearly illustrate this point, the data from several studies in which sleep-deprived helicopter pilots were tested under either dextroamphetamine or modafinil were combined and analyzed in a single unified effort. In addition, the more recently-completed study on the effects of lower-dose modafinil on sleep-deprived fighter pilots will be noted, but for several reasons that will not be detailed here, the fighter-pilot data will not be included in the integrated analysis.

2.0 METHODS

The five helicopter-pilot investigations were conducted at the U. S. Army Aeromedical Research Laboratory in Fort Rucker, AL, USA. Data analyses and reports were completed at the U. S. Air Force Research Laboratory in Brooks City-Base, TX. Data were collected under virtually identical research protocols. For the present analyses, the final 24 hours from the 64-hour dextroamphetamine study were excluded.

2.1 Participants

A total of 34 UH-60 helicopter pilots were tested. The mean age was 31 years, and the mean flight experience was 1,238 hours. Of the 34 volunteers who were evaluated, 7 were female. All volunteers passed a medical prescreen (to rule out significant illnesses of any type, sleep difficulties, allergic reactions to medications, etc.) prior to admission into the protocols. Participants were not permitted to ingest caffeinated products at any time.

2.2 Materials

2.2.1 Dose Preparation

In the dextroamphetamine studies, two orange gelatin capsules were administered at each dose time (midnight, 0400, and 0800) with 8 oz. of orange juice. Each active capsule contained one 5-mg tablet of dextroamphetamine (two were given per dose), and each placebo capsule contained lactose powder. In the modafinil study, two 100-mg white tablets were administered at each dose time (2300, 0300, and 0700). The active tablets matched the placebo tablets in appearance. Each dose was given with a glass of water.

2.2.2 UH-60 Simulator

Simulator flights (performed in four of the five studies) were conducted in a UH-60 simulator (CAE-Link Corporation, Model Trainer ASSY-2B38, Binghampton, NY) with computer-generated visuals (set for standard daytime flight), a six-degree-of-freedom motion base, and a multi-channel data acquisition system. Computerized flight performance data (e.g., headings, altitudes, airspeeds, turn rates, etc.) were collected and stored on a Digital Equipment Corporation (Nashua, NH) VAX 11/780.

2.2.3 UH-60 Aircraft

All aircraft flights (performed in one of the four dextroamphetamine studies) were conducted in a specially-instrumented UH-60 helicopter (Sikorsky Aircraft, Stratford, CT) equipped with a computerized flight monitoring system which recorded the same aspects of pilot performance that were collected in the simulator studies.

2.2.4 Electroencephalographic (EEG) Evaluations

EEGs were recorded via Grass (Quincy, MA) E5SH electrodes (filled with SigmaGel electrolyte) from electrode site C_Z. Data were amplified and stored on a Cadwell Spectrum 32 (Kennewick, WA). The low and high filters were set at 0.53 and 20 Hz, respectively, and the 60 Hz notch filter was used.

2.2.5 Profile of Mood States (POMS)

Mood was assessed with the vigor scale from the POMS (49), a 65-item test.

2.3 Procedure

2.3.1 Overview

The overview here is based on the schedule used for the 40-hour continuous-wakefulness studies. Note that there was an extra sleep-deprivation day (excluded from the present data analysis) and one extra recovery day (between the deprivation periods) in the 64-hour dextroamphetamine study. Volunteers arrived at the Laboratory on Sunday for prescreening and preparation. Training sessions were conducted at 0900, 1300, and 1700 on Monday (training day) following the administration of a 2.5 mg test dose of dextroamphetamine (in the case of the dextroamphetamine studies). On Tuesday (control) and Thursday (control), there were testing sessions at these times as well. On Wednesday (the deprivation day in the first cycle), and on Friday (the deprivation day in the second cycle), testing sessions began at 0100, 0500, 0900, 1300, and 1700. In each session, flight performance was assessed first, EEG next, and self-rated vigor last. On the sleep-deprivation days, drug or placebo doses were administered at 0000, 0400, and 0800 in the dextroamphetamine studies and

at 2300, 0300, and 0700 in the modafinil study. At each dose time, subjects received either the stimulant or matching placebo. Either placebo or stimulant was administered at every dose time within a specific deprivation cycle (e.g., subjects either received stimulant three times consecutively or placebo three times consecutively). The studies were double blind and counterbalanced.

2.3.2 Flight Performance

Regardless of whether subjects participated in one of the simulator studies or the in-flight study, the core maneuvers in the flight profiles were virtually identical. There were several maneuvers of the type typically flown in a UH-60 helicopter (and described further in the data analysis section). Each 1-hour flight was coordinated by a safety pilot (or a pilot/console operator in the simulator) who instructed the subjects through the maneuvers. Based on the data collected between each maneuver's start and stop points, scores ranging from 0-100 (with 100 reflecting near perfect accuracy) were calculated for a variety of measures. These scores, based upon the extent to which subjects deviated from ideal target values, expressed how well subjects maintained specified headings, altitudes, airspeeds, and other parameters.

2.3.3 EEG Evaluations

EEG sessions occurred shortly after the flights. In each session, data were collected under eyes open and eyes closed conditions, for 1.5-2.0 minutes per condition. Data recorded from C_z (the vertex site) will be reported. Absolute power values expressed in microvolts squared were calculated (via Fast Fourier Transformations) for each of four frequency bands: delta (1.0-3.5Hz), theta (3.5-8.0 Hz), alpha (8.0-13.0 Hz) and beta (13.0-20.0 Hz), but only theta activity will be reported here.

2.3.4 POMS

The POMS was given approximately one hour after the EEG. Subjects indicated on a standardized form how well each of 65 mood adjectives described the way he/she was presently feeling. Vigor scores were calculated using standardized scoring techniques.

2.3.5 Data Analysis

All of the data were analyzed with BMDP4V, repeated measures analysis of variance (ANOVA). The basic design for the flight, EEG, and POMS data was a mixed-factorial ANOVA with one grouping factor (study) and two within-subjects factors (drug and session). However, for the flight performance data, an additional "maneuver" factor with 6 levels was added. Performance was separated into each maneuver type--straight-and-level (SL), left standard-rate turn (LSRT), right standard-rate turn (RSRT), straight climb (CLIMB), straight descent (DESCENT), and left-descending turn (LDT). For the EEG data, an additional factor for eyes (closed/open) was added.

3.0 RESULTS

Flight performance, EEG, and POMS data were analyzed in three separate mixed-factorial analyses of variance. An overall depiction of the combined data is presented in Figure 1.

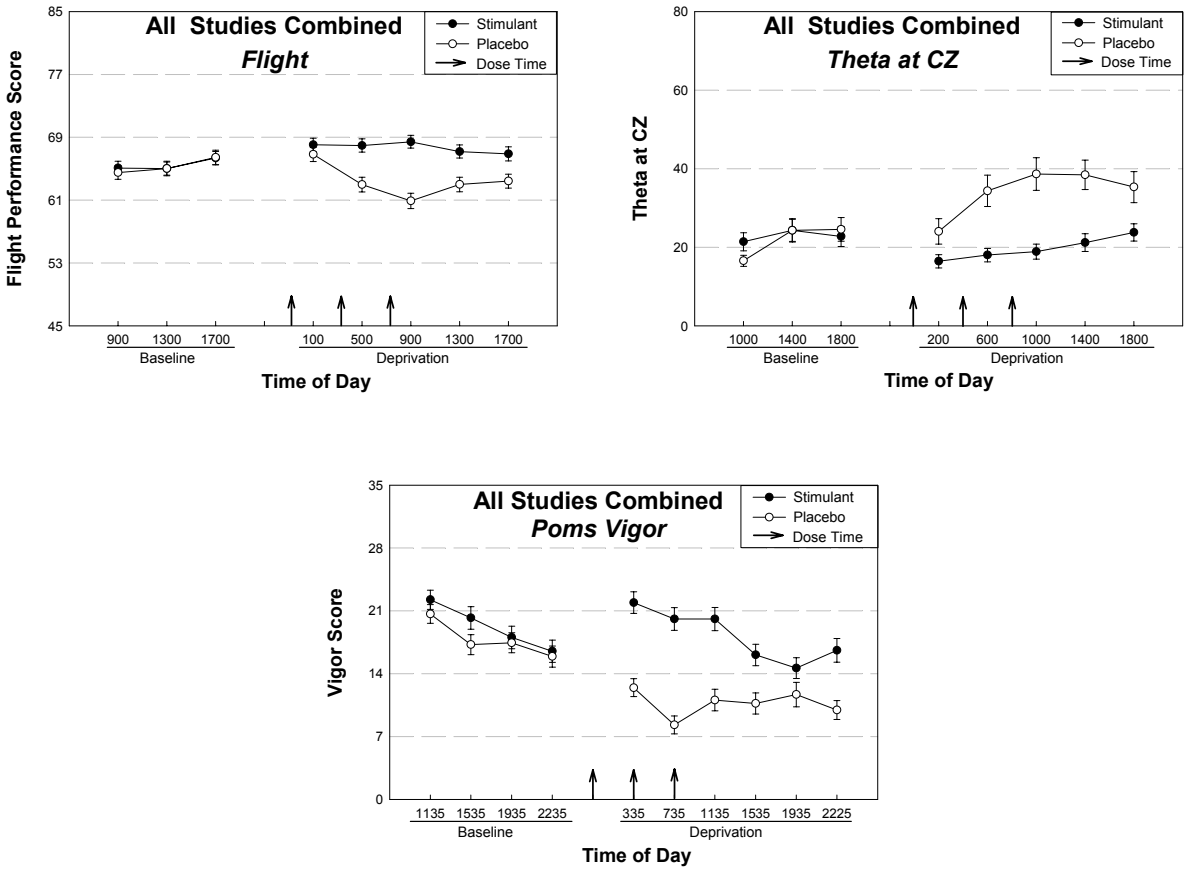

Figure 1: A Summary of the Flight Performance, EEG, and POMS Data from all Studies.

3.1 Flight Performance

The 4-way ANOVA for study, condition, session, and maneuver revealed several effects, but only the drug-related (condition-related) main effects and interactions are presented here for the sake of brevity. At the outset, it should be noted that the overall performance in the modafinil group did not differ systematically from performance in the dextroamphetamine groups. There was a study-by-condition-by-session interaction on overall flight performance due to a smaller effect size in the 40-hour in-flight dextroamphetamine study ($p=.0554$) in comparison to the remaining four studies. However, as can be seen in Figure 2, the differences between the stimulant and placebo conditions in the in-flight study were similar to what was observed in the other studies. There was an overall condition-by-session interaction because the combined stimulant effect produced superior performance relative to placebo at all five of the sleep-deprivation sessions ($p<.05$) while no differences occurred during the baseline (see figure 1, top left). There also was a main effect on the condition factor due to better performance under the stimulants (63.4) than under placebo (61.8). Note that the baseline phase was included in these overall means, making the stimulant effect appear smaller than it actually was.

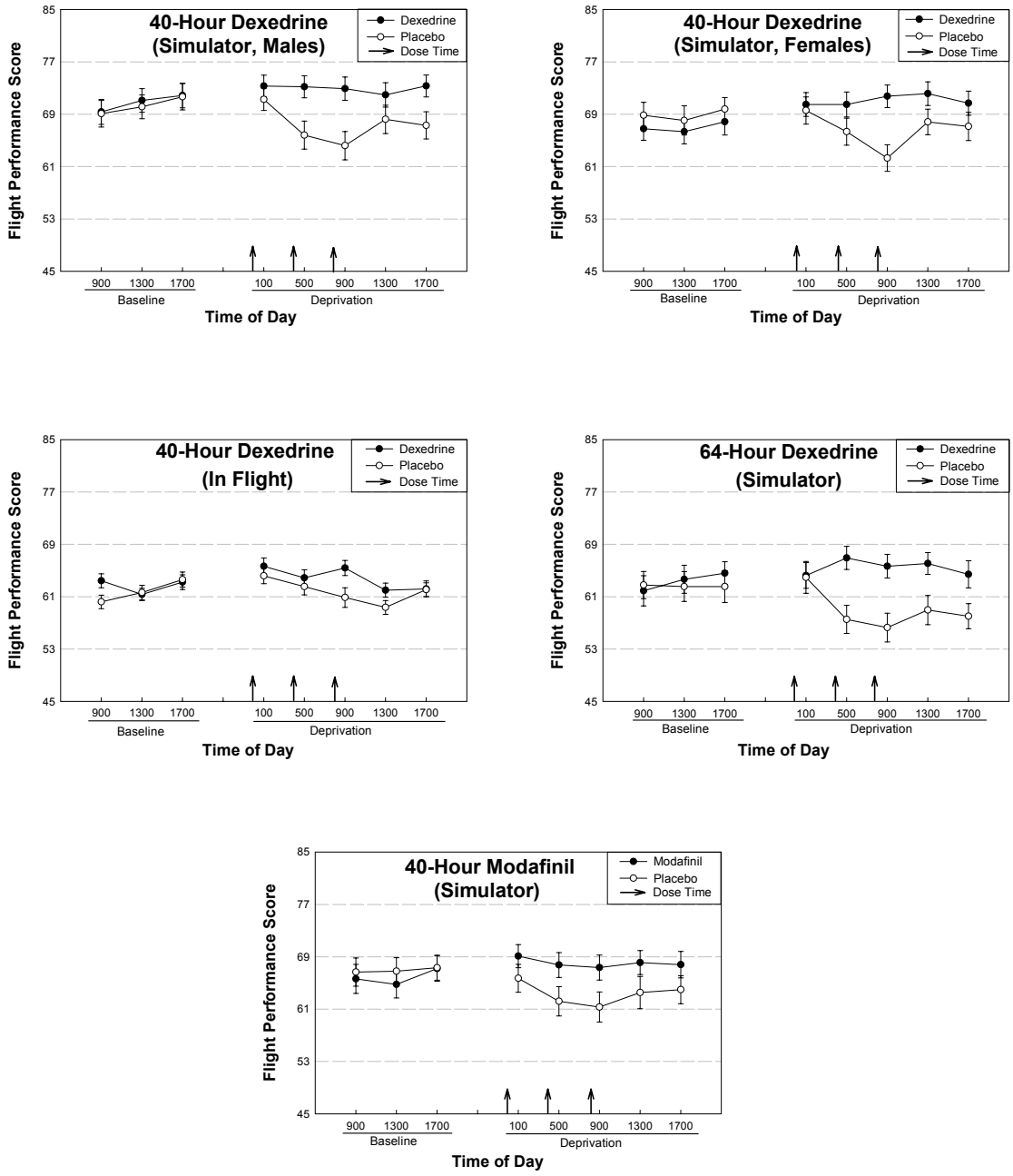

Figure 2: The Condition-by-Session Interaction on Flight Performance.

3.2 EEG Theta

The 4-way ANOVA for study, condition, session, and eyes indicated a variety of effects on absolute EEG theta power (3-8 Hz). In the present report, only the drug-related (condition-related) effects are presented. There were no differences across the five studies, indicating reliable stimulant-versus-placebo effects in each case (see figure 3). There was a condition-by-session interaction attributable to attenuation of theta activity at

each of the sleep-deprivation sessions under the stimulant relative to placebo ($p<.05$). There also was a condition main effect across all of the studies collapsed due to less theta activity under the stimulants than under placebo (20.8 mV^2 versus 29.5 mV^2). As was the case with the flight data, this difference shows the positive effects of the drugs, but underestimates the overall stimulant effect because the baseline sessions and the deprivation sessions were averaged together.

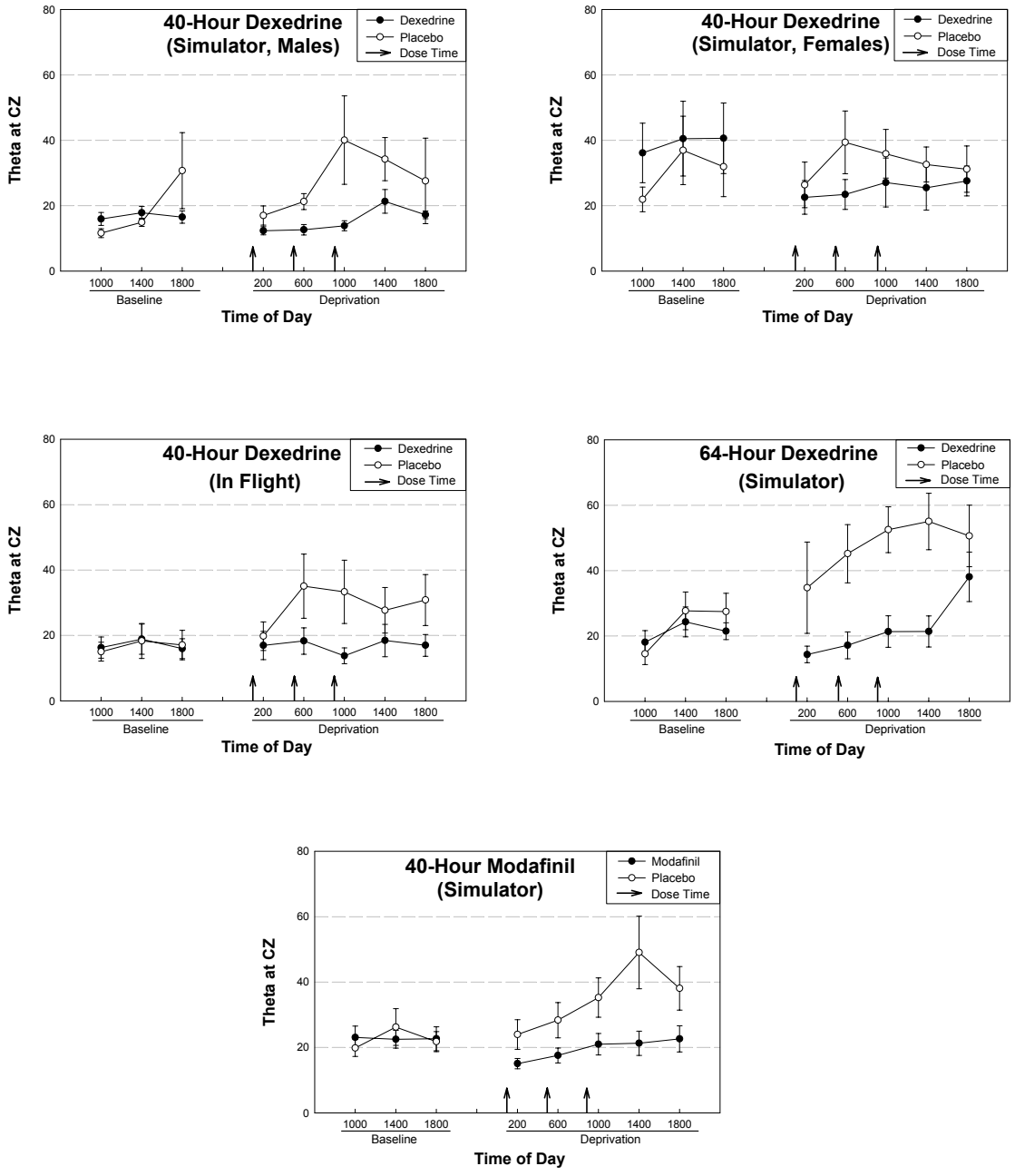

Figure 3: The Condition-by-Session Interaction for Theta Activity for Each Individual Study.

3.3 POMS Vigor

POMS vigor/activity scores were analyzed with an ANOVA for study, drug, and time (or session). Analyses of these scores indicated there were no overall differences in the size of the stimulant/placebo effects across the five studies (see figure 4). However, there was a significant condition-by-session interaction which was due to greater scores under the stimulant condition than the placebo condition at each of the deprivation sessions, whereas no differences occurred during the baseline (see figure 1, bottom). In addition, there was a condition main effect because, overall, vigor/activity scores were greater under the stimulant condition than under the placebo condition (18.33 versus 13.53, respectively).

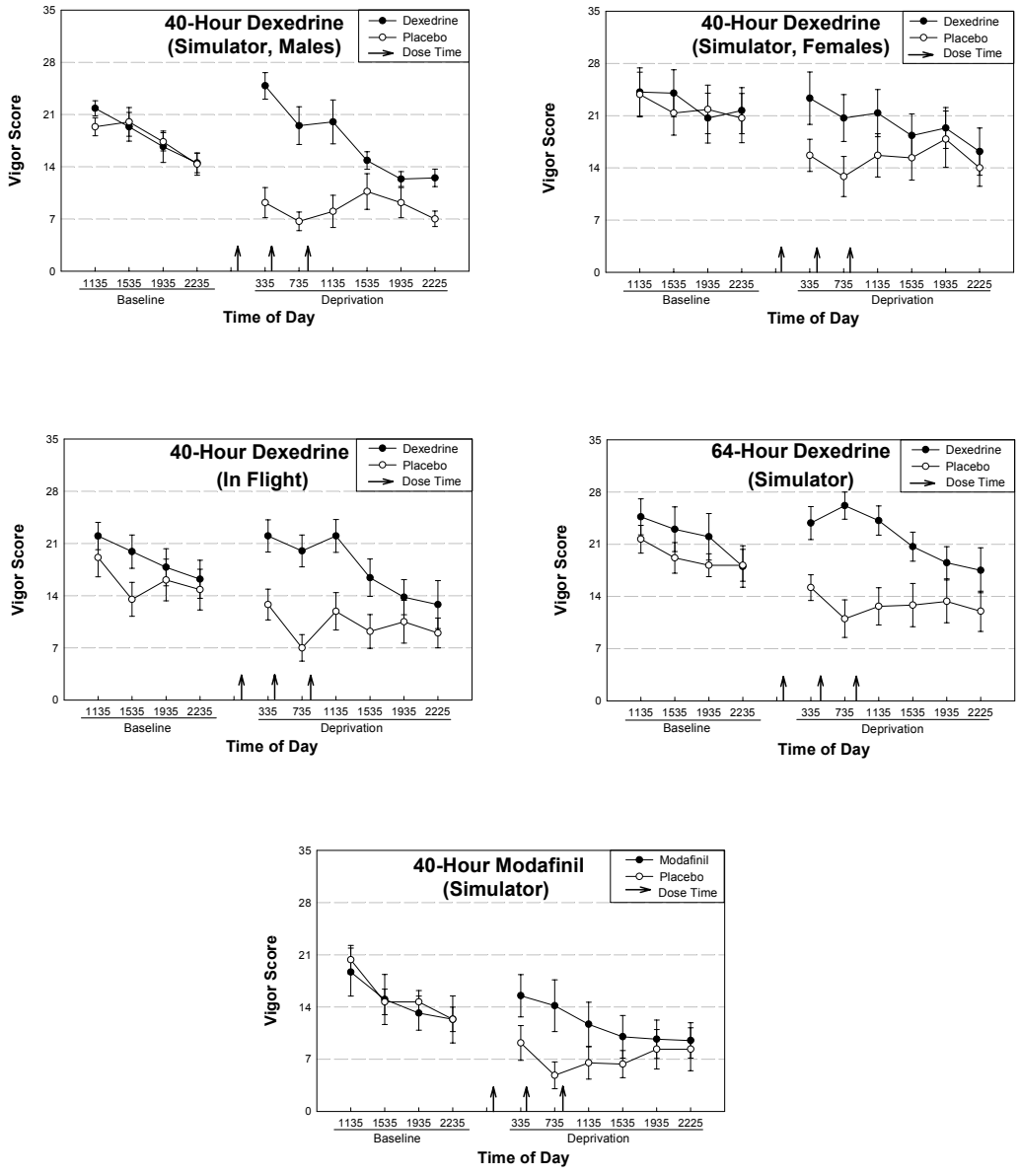

Figure 4: A Depiction of the Condition-by-Session Interaction for POMS Vigor/Activity Scores for Each of the Individual Studies.

3.4 Summary

It is important to emphasize that the results were remarkably consistent across the previously-discussed studies despite the relatively small number of subjects evaluated in each. In every case, the stimulant condition was better than the placebo condition. Also, it should be noted that the modafinil results (with 200-mg doses) reported here are consistent with the recently obtained findings from a new fighter-pilot investigation of low-dose (100 mg) modafinil (administered after 17, 22, and 27 hours of continuous wakefulness) (39). Unfortunately, due to slight differences in the experimental designs of the primary studies reported here and the fighter-pilot investigation, it was not possible to include the new fighter-pilot findings with the helicopter-pilot assessments. However, the percent-change-from-baseline data on fighter-pilot flight performance and EEG theta are presented below in figure 5 for visual comparison.

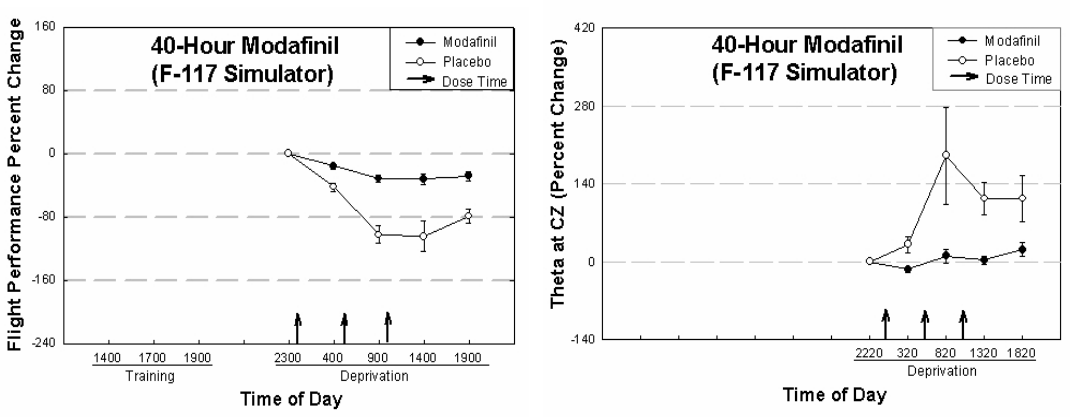

Figure 5: Flight Performance and EEG Theta Findings from a Recently-Completed Study on the Alertness-Enhancing Characteristics of Repeated 100-mg Doses of Modafinil in Fighter Pilots (the 2300 Session was used as a Baseline).

4.0 DISCUSSION

This composite analysis of data from five previously-conducted stimulant studies supported and extended earlier conclusions that both dextroamphetamine and modafinil are useful for the short-term management of fatigue in sleep-deprived aviators. Both stimulants were particularly helpful after 20 to 29 hours without sleep (between 0300 and 1200), but beyond this time as well. These results were reliable across investigations.

The only instance of a difference in the magnitude of drug-by-session effects across studies was related to flight performance in the simulator versus the aircraft environment. Although the stimulant condition was associated with sustained performance throughout all of the assessments, actual in-flight testing was less sensitive to the positive impact of the drug (and the negative impact of sleep loss) compared to simulator testing. As has been discussed elsewhere (50), this probably resulted from increased physiological activation in the aircraft versus the simulator (since the consequences of a mistake are more serious in the in-flight environment). Such an arousal increase tends to preserve performance under the placebo condition, resulting in smaller differences between the placebo and stimulant conditions.

Despite this effect, the overall flight data showed substantial performance declines under placebo at the deprivation sessions, while performance under the stimulants did not. This finding, with short-interval 10-mg

doses of dextroamphetamine and 200-mg doses of modafinil, extends those of Pigeau et al. (51) who reported that widely spaced 20-mg doses of dextroamphetamine and 300-mg doses of modafinil were effective for attenuating initial performance declines and for recovering already-degraded performance. In the present study, performance under placebo declined sharply (particularly after 0100), reaching its lowest point by 0900, before recovering partially later in the day. Under stimulant, flight skills remained at or above normal throughout.

The EEG data revealed that central-nervous-system activation was affected similarly in that dextroamphetamine and modafinil preserved EEG activity at more normal levels compared to placebo. Generally speaking, sleepiness and fatigue are known to accentuate the amount of slow-wave brain activity (52), and increased theta activity has been associated with generalized performance decrements on cognitive tasks (53). Thus, the stimulant-related attenuation of theta activity during sleep deprivation coincides well with the flight-performance results.

The subjective reports of vigor demonstrated that the stimulant condition also was associated with a perceived sustainment of energy levels compared to placebo. While there were sleepiness-related overall reductions in vigor scores under both drug and placebo, the effect was attenuated by the stimulants.

5.0 SUMMARY AND CONCLUSIONS

Dextroamphetamine has for years been proven effective for maintaining the performance of fatigued but otherwise normal personnel (37, 54), and modafinil is gaining acceptance as a dextroamphetamine alternative (55, 51, 56). This is despite the fact that neither compound has been approved for this specific purpose by the U.S. Food and Drug Administration. Although it is true that long-term, indiscriminate administration of these or any other alertness-enhancing substances may pose both physical and psychological risks, there is no indication that aviators have abused or will abuse such compounds under controlled circumstances. In light of this fact, and in light of the present data which demonstrate the efficacy of these compounds for sustaining the alertness and performance of sleep-deprived pilots, it appears that well-controlled administration of dextroamphetamine and modafinil should be considered appropriate for the short-term management of fatigue in select situations. Clearly, it is better to pharmacologically sustain wakefulness than to run the risk that pilots will inadvertently fall asleep at the controls. However, it must be reemphasized that no stimulant can replace effective crew-rest scheduling or provide a substitute for restful, restorative sleep.

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