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Effects of Tyrosine, Phentermine, Caffeine D-amphetamine, and Placebo on Cognitive and Motor Performance Deficits During Sleep Deprivation

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Cognitive and motor performance are critical in many circumstances and are impaired by sleep deprivation. We administered placebo, tyrosine 150 mg/kg, caffeine 300 mg/70 kg, phentermine 37.5 mg and D-amphetamine 20 mg at 15.30 h following overnight sleep deprivation and compare their effects on cognitive and motor performance in healthy young men. Tests of visual scanning, running memory, logical reasoning, mathematical processing, the Stroop task, four-choice serial reaction time, time wall take, pursuit tracking, visual vigilance, Trails (B) task and long-term memory were evaluated at standardized intervals before, during and after sleep deprivation and drugs. Performance decrements with sleep deprivation occurred in visual scanning, running memory, logical reasoning, mathematical processing, the Stroop test, the time wall test, tracking and visual vigilance. Interestingly, with sleep deprivation some tests improved and others did not deteriorate. Improvements with medication following sleep deprivation were seen in running memory, logical reasoning, mathematical processing, tracking and visual vigilance. Although less effective than D-amphetamine, tyrosine improved performance on several tests. We conclude that all drugs tested improved at least some aspects of cognitive and motor performance after sleep deprivation. As a naturally occurring amino acid, and thus amenable to nutritional strategies, tyrosine may deserve further testing.

Keywords: Diurnal rhythm; Sleep deprivation; Sleep drive; Sleep quality; Sleep quantity; Polysomnography

INTRODUCTION AND BACKGROUND

In his review of the accumulated experimental evidence concerning the effects of long-term sleep deprivation on human performance, Dinges (1992) proposed that performance failures during sleep loss could be organized as follows: cognitive slowing; memory encoding, storage, and retrieval problems; decrements in vigilance; deterioration in optimum speed of response and reaction time; increased periods of delayed or nonresponding; and, an increased frequency of false responses. The common cognitive phenomenon that relates to each of these decrements in performance is a deficit in attention.

Although performance deficits due to long-term, continuous sleep deprivation can be overcome by sleep (Dinges, 1992; Bonnet, 1994), this remedy is not always available and people may be required to perform tasks while sleep-deprived. For example, continuous and sustained military operations require performance while sleep deprived. In situations such as these, it would be desirable to find safe, acceptable and readily available methods of improving performance caused by sleep deprivation. The CNS-activating substances, D-amphetamine and caffeine, have a history of use and effectiveness in sleep-deprived situations. D-amphetamine has been shown in numerous research studies to reverse the deficits in cognitive performance due to sleep deprivation (Newhouse *et al.*, 1989; 1992; Caldwell *et al.*, 1995; Pigeau *et al.*, 1995). The effects of caffeine on various aspects of human behavior, such as mood, alertness, vigilance and sleep have been well documented (Lieberman, 1992). Caffeine has been shown to reduce deficits in cognitive

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performance during sleep deprivation (Bonnet and Arand, 1994; Bonnet *et al.*, 1995), and to improve alertness during sleep deprivation as measured by mood ratings (Penetar *et al.*, 1993).

The present study was designed to extend previous investigations on the effects of CNS-activating substances for overcoming deficits in human performance due to sleep deprivation. Our focus was performance in military settings which require performance during sleep deprivation. We also sought to evaluate a potential nutritional approach to improving performance during sleep deprivation, and we chose tyrosine for this evaluation. It has been hypothesized that in conditions where stress is operant, catecholaminergic neurons would be more likely to convert tyrosine to dopamine and norepinephrine, neurotransmitters that might improve performance (Lieberman, 1994). Tyrosine has been evaluated in only one prior study (Neri *et al.*, 1995) of performance in the sleep deprived state. In that study, tyrosine in a 150 mg/Kg dose ameliorated the performance decline in a psychomotor task and a vigilance task.

More specifically, our study investigated and compared the effects of placebo versus D-amphetamine, caffeine, phentermine, and tyrosine on cognitive and motor performance during long-term sleep deprivation. We administered these substances, and a placebo, according to a double blind, randomized procedure to healthy male subjects who were sleep deprived for 32 h before the substances were administered (Waters *et al.*, 2000). Total sleep deprivation was 40.5 h. In this paper, we report results from a battery of tests and cognitive and motor performance at various times prior to and during sleep deprivation. Data pertaining to the effects of these substances on sleep parameters and endocrine responses have been reported previously (Waters *et al.*, 2003).

METHOD

Subjects

Subjects for this study were 76 healthy male volunteers who ranged in age from 18–35 years and who had a body mass index (BMI) range of 20–27 kg/m. Details about recruitment, screening, and Institutional Review Board review are provided elsewhere (Waters *et al.*, 2003) Respondents to the advertisements were excluded if they had any medical disorder that would interfere with interpreting the results of the study, a history of mental or sleep disorder, evidence of recent or remote substance abuse, or evidence of sensitivity to any CNS-activating medications.

The subjects selected for participation in this study were paid for their participation. The experimental protocol, informed-consent form, and advertisements were approved by the Louisiana State University Institutional Review Board and by the Department of Defense Human Subjects Research Review Board. Only those subjects who successfully completed the medical and psychological evaluation were eligible for participation in the study.

Experimental Protocol

A detailed presentation of the protocol is presented elsewhere (Waters *et al.*, 2003). The experiment was conducted in a sleep laboratory containing two private rooms and an observation area. Two subjects were studied simultaneously and were under direct observation throughout the 4-day study period. The study protocol allowed minimal time for personal needs. Figure 1 presents a flow diagram of the experimental protocol followed for each subject. This protocol consisted of four phases: Baseline (Days 1–3), Sleep Deprivation (Days 3–4), Medication (Day 4) and Recovery (Day 5).

Baseline Days

Day 1, which began on Wednesday at 20.00 h, Day 2 and most of Day 3 (until 23.30 h), involved obtaining baseline measures on sleep and performance measures. Shortly after arriving at the sleep laboratory at 21.00 h on Wednesday night, each subject was introduced to the performance test battery and engaged in a practice session of each test in the battery. Performance during this introductory session was not scored. The subject went to bed to sleep in his room in the sleep laboratory at 23.30 h.

On Day 2, the subject was awakened at 07.00 h and ate a prepared breakfast in his room. At 09.00 h, the first baseline performance test battery was given. The same battery was given again at four-hour intervals corresponding to 13.00, 17.00 and 21.00 h. Each testing session took approximately 1.25 h. Lunch and dinner were served to the subject at 12.00 and 19.00 h, respectively. As on Day 1, the subject went to bed at 23.30 h.

The protocol for Day 3 was the same as Day 2 until after the performance test session at 21.00 h. Instead of going to bed at 23.30 h, the subject was not permitted to sleep either during the night or during the following day until 23.30 h on Day 4.

During the Baseline Days, performance test data were collected during eight sessions. Pilot testing of the battery had indicated that this amount of repetition was sufficient to overcome learning effects

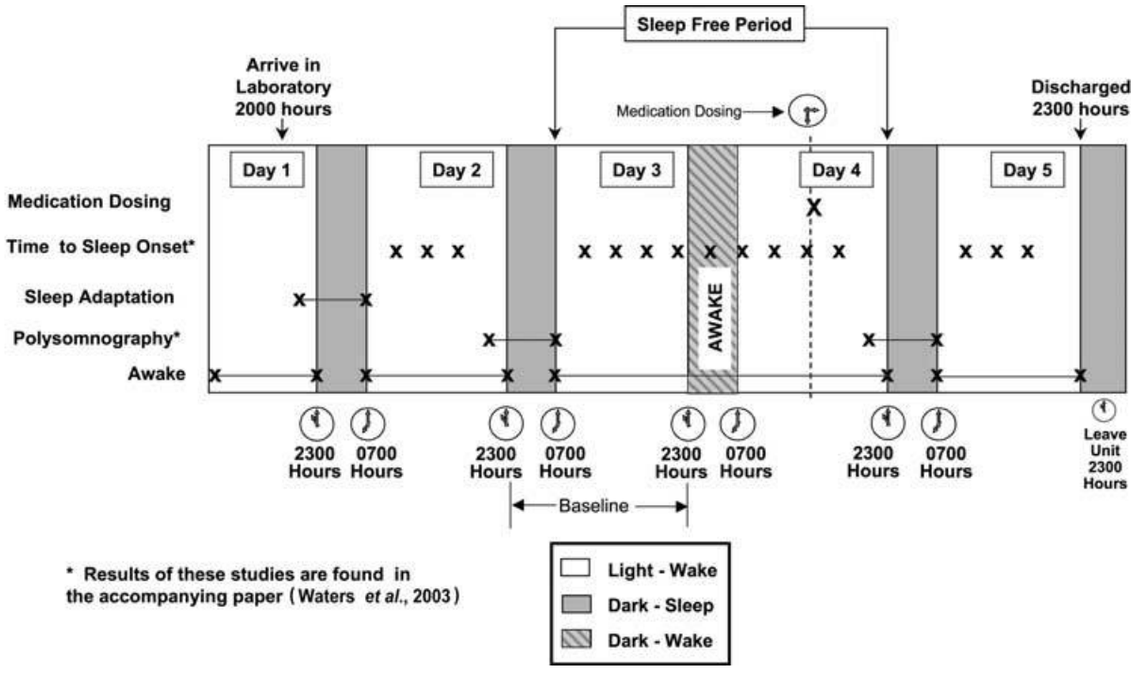

FIGURE 1 A diagram of the study protocol. Two volunteer subjects entered the sleep laboratory for the four-night protocol on Wednesday. After an habituation night (day 1), volunteers began a baseline testing day and night (day2). They were deprived of sleep on Night 3 while being continuously observed. The medication dosing occurred at 15:30 h on day 4. On Night 4, recovery sleep was monitored and patients were tested for recovery effects on day 5.

for those tests in the battery in which a learning effect could occur.

Sleep Deprivation Day

The performance test battery was administered every 4 h to the subject during the night of no sleep, with the first test given at 01.00 h. The performance test battery was administered at the same times during the sleep-deprived day as the baseline days.

At 15.30 h, when the subject had gone 32.5 h without sleep, the drug doses were administered (Waters *et al.*, 2003). Two performance test sessions followed at their regular times (17.00 and 21.00 h), which provided an opportunity to assess drug effects on the performance tests at 1.5 and 5.5 h after the drugs were administered. Both sessions were well within the most active periods of the administered drugs. The subject was allowed to go to bed to sleep at 23.30 h.

Sleep Deprivation Recovery Day

The subject was awakened at 07.00 h on Day 5, which was the regular wake-up time for days following a night of sleep. Four additional performance test sessions were held during the day at the same times as they had occurred on the previous three days beginning at 09.00 h. The subject left the sleep laboratory to go home at 23.30 h.

Performance Test Battery

Eleven performance tests were selected for the test battery based on several criteria. The tests related to a variety of cognitive, attention, perceptual and/or motor characteristics associated with CNS functions influenced by the nutritional/pharmacological substances used in this study. The tests also were related to specific aspects of human performance situations found in military contexts, although all have civilian performance analogs as well. Finally, most of the tests have a history of showing human performance deficits due to long-term sleep deprivation.

The performance tests in the test battery were (in the order administered):

Visual Scanning Task

This test required the subject to scan a matrix of letters to locate the letter K. The computer based version of this task, developed in our laboratory, was based on a test proposed for the Walter Reed Performance Assessment Battery (PAB). Subjects performed 20 trials per session. The performance measure was the amount of time to locate the correct letter.

Running Memory Task (From the Army Neuropsychological Assessment Metric—ANAM)

Subjects viewed a series of 80 individually presented letters. When each letter was presented, the subject pressed the appropriate mouse key to indicate if the presented letter was the same or different from the letter shown just before it. Performance measures were percent correct and response delay time (RT).

Logical Reasoning Task (Grammatical Version) (From PAB)

Subjects viewed a statement (e.g. A is followed by B). Then a letter pair was presented (e.g. AB). The subject responded by clicking the appropriate mouse button to indicate true or false about whether or not the letter pair relationship was congruent with the preceding statement. Subjects performed 80 trials per session. Performance measures were response latency per response (RT) and number of errors per session.

Mathematical Processing (Addition/Subtraction) (from ANAM)

Subjects tried to solve a simple addition or subtraction problem and respond whether the answer is greater than or less than five by pressing the appropriate mouse button. Subjects performed 80 trials per session. Performance measures were percent correct and average response latency (RT) per correct response.

Stroop Task (from PAB Color Test)

Subjects viewed the words RED, GREEN and BLUE on the computer monitor, one at a time. On each presentation, the letters could be red, blue, or green in color. The subject responded according to the color of the letters by pressing the appropriate key on the keyboard. Subjects performed 80 trials per session. Performance measures were percent correct for congruent and incongruent word-color items, and average response latency (RT).

Four-choice Serial Reaction Time Task (from PAB)

Subjects saw a blinking + sign in one of four quadrants on the computer monitor. The subject responded as quickly as possible by pressing the corresponding designated keyboard key. The + remained visible until a key was pressed, and then randomly appeared in one of the four quadrants for the next trial. Subjects performed 75 trials per session. The performance measure was reaction time (RT) for correct responses.

Time Wall Task (from PAB)

In this test of time estimation, subjects observed an object (a brick) descending from the top of the computer monitor screen at a constant rate toward a target at the bottom of the screen. The target disappeared behind a brick wall about two-thirds of the way down the screen. The subject responded by pressing a designated key at the exact time that he estimated the object would contact the target. Subjects performed 20 trials per session. The performance measure was the amount of timing error.

Pursuit Tracking Task (from ANAM)

Two cursors were shown in the center of the computer monitor. The bottom cursor was the target cursor. The subject moved the mouse to make the top cursor follow the target cursor as closely as possible as it moved horizontally left and right at a constant rate. Tracking was continuous for 3 min. The performance measure was based on the amount of error per unit of time for subject cursor deviations from the target cursor.

Visual Vigilance Task (Lieberman **et al.***, 1998)*

Subjects observed a darkened computer monitor for 40 min. At random and infrequent intervals, a small, dim light appeared somewhere on the monitor. The subject depressed the appropriate key when he detected the light. Performance measures were the number of correct responses (out of 40 possible) and the average response latency (RT) for correct responses.

Trails (B) Task

The subject was given a sheet of paper on which was a series of randomly arranged consecutive letters and numbers. The subject used a pencil and, starting at the number 1, traced a path between each succeeding number and letter in alternating fashion (i.e. 1-A-2-B, etc.). The performance measure was the time to completion.

Long-term Memory Task

Subjects were verbally given a sentence at the beginning of the test session. Included in the sentence was a variety of specific factual information. Each sentence contained 12 bits of information. At the end of the test session (approximately one and a half hours), the subject was asked to write down as much of the sentence as he could remember. The performance measure was the number of correct information bits recalled.

Drug Administration

D-amphetamine, 20 mg; phentermine, 37.5 mg; caffeine, 300 mg/70 kg; tyrosine, 150 mg/kg; placebo, 250 mg of cellulose and placebo were given in 500-mg opaque gelatin capsules as described previously (Waters *et al.*, 2003). Medication was given at 15.30 h on Day 4. A light carbohydrate snack was served with the capsules to prevent gastrointestinal discomfort. A similar snack was given at the same time on the other days of the study.

Statistical Analysis

The statistical analysis involved assessing performance data for all 11 performance tests for 10 of the 18 testing sessions. Only the four sessions on Day 3 were considered as baseline performance. Day 5 sessions were excluded from the analysis as these sleep deprivation recovery data were not critical for addressing the performance questions of interest for this report.

Statistical Model

The first eight sessions involved all subjects prior to their random assignment to the five treatment conditions. Because of the subject screening and selection procedures, it was assumed that all subjects were randomly sampled from a homogeneous population of healthy males of ages 18–35. Accordingly, the population mean for the pre-drug period was modeled as an eight-dimensional fixed unknown vector parameter. After the subjects were randomly assigned to the five treatment groups, the population means of each group were modeled as a two-dimensional fixed unknown vector of parameters. All performance variables were analyzed using Proc Mixed in SAS Version 6.12 using a repeated measures design with repetitions over 10 sessions. All multiple comparisons were adjusted according to Bonferroni's inequality.

Choice of Response Variables for Analysis

In seven of the eleven performance tests, response delay measures (i.e. reaction time, response latency) was a dependent variable. For these tests, each testing session consisted of as many as 80 trials, depending on the test. To eliminate the influence of outliers and to summarize the response delay variable for analysis purposes, the 10% trimmed mean was used as the performance variable for each subject for each session. A trimmed mean was not necessary for the other dependent variables (i.e. percent correct, number of correct hits, and number of errors).

RESULTS

Sleep Deprivation Effects

Response delay measures (reaction time, response latency) showed the most consistent sleep deprivation effects prior to drug administration. To examine most specifically the effect of continuous sleep deprivation on performance during the immediate pre-drug session (Day 4, 13.00 h), comparisons were made between this session and the time-matched pre-deprivation test session (Day 3, 13.00 h). The means for these tests for the two testing sessions are presented in Table I. Based on *post hoc* *t*-test analyses of these comparisons, using Bonferroni probability adjustments, the 28 h of sleep deprivation at the 13.00 h testing session on the Day 4, led to significant increases in the response delay times for each of the following tests:

TABLE I Effects of 30 h of sleep deprivation on performance of tasks used in this study

Task/Dep. Meas.	Day 3 13:00 h (6 h no sleep)	Day 4 13:00 h (30 h no sleep)	% Performance Decrement (for significant effects)
Vis. Scan./*Detec. time*	10.81 s	10.71 s	
Run. Memory/*RT*	0.46 s	0.48 s*	4.0%
Run. Mem./*% corr.*	66.7%	66.7%	
Logic. Reas./*Res time*	3.12 s	3.71 s*	15.7%
Logic. Reas./*% corr.*	66.4%	66.3%	
Math Proces./*RT*	1.51 s	1.57 s*	4.0%
Math Proces./*% cor.*	66.5%	65.4%	
Stroop/*RT*	0.52 s	0.52 s	
Stroop/*% cor.*	70.3%	70.0%	
4-choice SRT/*RT*	0.37 s	0.37 s	
Time Wall/*iming err*	0.27 s	0.20 s	
Tracking/*error*	2.13	2.19*	2.7%
Vis. Vigilance/*RT*	1.12 s	1.28 s*	12.0%
Vis. Vigilance *hits/40*	35.7 hits	26.7 hits*	26.7*
Trails (B)/*comp. time*	40.3 s	39.4 s	
LTM/*no. correct*	7.5 items	6.9 items	

*Indicates statistically significant ($p < .05$) differences that show sleep deprivation *performance deficits*.

Running Memory, $t(75) = 3.37,\ p = 0.0002$; Logical Reasoning, $t(75) = 5.63,\ p = 0.0002$; Mathematical Processing, $t(75) = 2.63,\ p = 0.021$; and, Visual Vigilance, $t(75) = 7.09,\ p < 0.0001$. The sleep deprivation effect was also assessed by simultaneously comparing performances between Days 3 and 4 for the 09.00 h and 13.00 h test sessions. Significant response delay deficits were found for the same four tasks: Running Memory, $F(2,75) = 10.19, p < 0.0001$; Logical Reasoning, $F(2,75) = 27.89,\ p < 0.0001$; Mathematical Processing, $F(2,75) = 7.62,\ p = 0.001$; and Visual Vigilance, $F(2,75) = 39.95, p < 0.0001$.

Performance measures related to response correctness (percent correct, amount of error, number of hits) also are presented in Table I. *Post hoc t*-test analyses, using Bonferroni probability adjustments, comparing the immediate pre-drug session (Day 4, 13.00 h) and its time-matched pre-deprivation test session (Day 3, 13.00 h), showed significant effects for the following tasks: Tracking, $t(75) = 2.98$, $p = .0038$, and the number of hits for Visual Vigilance, $t(75) = 8.13,\ p < 0.0001$. The results also showed statistically significant performance deficits due to sleep deprivation only for the amount of error for Tracking, $F(2,75) = 5.58,\ p = 0.0055$, and the number of hits for Visual Vigilance, $F(2,75) = 44.99$, $p < 0.0001$.

Drug Effects on Performance Deficits

Drug effects were assessed at 1.5 h (Day 4, 17.00 h) and 5.5 h (Day 4, 21.00 h) after drug administration (Day 4, 15.30 h). Statistical analyses compared performance at the two post-drug test sessions with the pre-drug, 30 h sleep deprivation, baseline test session (Day 4, 13.00 h). Table II shows the means and statistical effects for these comparisons for the tasks that showed performance deficits related to sleep deprivation. The following sections describe the pre-planned contrast analyses for each drug for these tasks.

Placebo

Administering a placebo following 30 h of sleep deprivation did not significantly change performance for tasks that showed sleep deprivation effects (with one exception): Running Memory RT showed improvement at +5.5 h, $t(74) = 2.31$, $p = 0.0476$).

Tyrosine

The results showed that tyrosine had less effect than D-amphetamine, phentermine, or caffeine, and when tyrosine did influence sleep deprived performance, it typically occurred during the later test session (5.5 h post-drug). This influence was shown for three tasks, including two dependent measures for one task: Running Memory RT, $t(74) = 2.83$, $p = 0.0122$; Logical Reasoning RT, $t(75) = 2.82,\ p = 0.0122$; Visual Vigilance RT, $t(75) = 2.86,\ p = 0.0054$; and, Visual Vigilance hits, $t(75) = 4.24, p < 0.0001$. The exception to this delayed influence was a significant benefit at 1.5 h post-drug for Mathematical Processing RT, $t(75) = 3.27$, $p = 0.0034$.

D-Amphetamine

D-amphetamine administered after 30 h of sleep deprivation significantly improved performance at both 1.5 and 5.5 h after drug administration on all the tasks, except one, that showed deficits during sleep deprivation. At 1.5 h after D-amphetamine (Day 4, 17.00 h), significant performance improvements were found for: Running Memory RT, $t(74) = 4.61$,

TABLE II For tasks showing performance deficits due to sleep deprivation, the drug effects on performance at 1.5 h post-drug administration (day 4/17:00 h) and 5. h post-drug administration (day 4/21:00 h)

	Pre-Drug Baseline						
Task (*Dep. Meas.*)	@ Day 3 [pre-deprivation]	@ 13:00 Day 4 [30 h no sleep]	Placebo @+1.5 h 5.5 h	Amph. @+1.5 h 5.5 h	Phenter @+1.5 h 5.5 h	Caffeine @+1.5 h 5.5 h	Tyrosine @+1.5 h 5.5 h
Run. Mem. (*RT*)			0.465	0.439*	0.433*	0.424*	0.469
	0.458	0.477	0.461*	0.434*	0.436*	0.432*	0.456*
Logic Reas. (*Resp. Time*)			3.683	3.532	3.355*	3.260*	3.705
	3.122	3.705	3.493	3.392*	3.329*	3.120*	3.328*
Math Proc (*RT*)			1.522	1.484*	1.437*	1.439*	1.463*
	1.507	1.572	1.558	1.447*	1.459*	1.481*	1.500
Tracking (*error*)			2.20	2.08*	2.07*	2.11*	2.14
	2.13	2.19	2.20	2.12*	2.07*	2.15	2.14
Vis. Vigil. (*RT*)			1.250	1.031*	1.079*	1.163	1.262
	1.123	1.276	1.288	1.059*	1.101*	1.144*	1.155*
Vis. Vigil. (*no. corr./40*)			28.6	37.0*	33.7*	36.8*	28.5
	35.7	26.7	27.9	35.2*	35.8*	36.1*	33.5*

All time measures are in s. *Indicates statistically significant improvement ($p < 0.05$) at 1.5 h and/or 5.5 h post-drug sessions (comparisons based on the Pre-Drug Baseline on Day 4).

$p = 0.0002$; Mathematical Processing RT, $t(75) = 2.94$, $p = 0.0088$; Tracking error, $t(75) = 3.91$, $p < 0.0004$; Visual Vigilance RT, $t(75) = 4.08$, $p = 0.0001$; and, Visual Vigilance hits, $t(75) = 7.07$, $p < .0001$.

At 5.5 h after D-amphetamine (Day 4, 21.00 h), significant performance improvements were found for: Running Memory RT, $t(74) = 6.43$, $p = 0.0002$; Logical Reasoning RT, $t(75) = 2.64$, $p = 0.02$; Mathematical Processing RT, $t(75) = 3.71$, $p = 0.0008$; Tracking error, $t(75) = 2.55$, $p < 0.026$; Visual Vigilance RT, $t(75) = 5.96$, $p = 0.0001$; and, Visual Vigilance hits, $t(75) = 5.89$, $p < 0.0001$.

The only exception to the consistent effects of D-amphetamine was at 1.5 h post-drug administration for Logical Reasoning RT, $t(75) = 1.41$, $p = 0.32$. However, it is important to note that this effect was statistically significantly improved 5.5 h after D-amphetamine.

Phentermine

Results with phentermine were similar to those with D-amphetamine. The statistical comparisons of task performances at the 1.5 and 5.5 h post-drug administration testing sessions with performances at the 13.00 h pre-drug baseline session showed that phentermine improved performance at both post-drug testing sessions for all tasks that demonstrated performance deficits due to sleep deprivation.

At 1.5 h post-drug administration (Day 4, 17.00 h), significant performance improvements were found for: Running Memory RT, $t(74) = 4.75$, $p = 0.0002$; Logical Reasoning RT, $t(75) = 2.64$, $p = 0.02$; Mathematical Processing RT, $t(75) = 4.04$, $p = 0.0002$; Tracking error, $t(75) = 4.44$, $p < 0.0002$; Visual Vigilance RT, $t(75) = 3.06$, $p = 0.0031$; and, Visual Vigilance hits, $t(75) = 4.56$, $p < 0.0001$.

At 5.5 h post-drug administration (Day 4, 21.00 h), significant performance improvements were found for: Running Memory RT, $t(74) = 5.57$, $p = 0.0002$; Logical Reasoning RT, $t(75) = 2.92$, $p = 0.0092$; Mathematical Processing RT, $t(75) = 2.87$, $p = 0.0106$; Tracking error, $t(75) = 3.91$, $p < 0.0004$; Visual Vigilance RT, $t(75) = 4.35$, $p = 0.0001$; and, Visual Vigilance hits, $t(75) = 5.89$, $p < 0.0001$.

Caffeine

The positive influence of caffeine on sleep-deprived performance was similar to that found for phentermine (with two exceptions) and amphetamine (with one exception). The only tasks not showing significant improvement with caffeine were Visual Vigilance hits at 1.5 h post-drug administration, and Tracking error at 5.5 h post-drug.

At 1.5 h post-drug administration (Day 4, 17.00 h), significant performance improvements were found for: Running Memory RT, $t(74) = 6.72$, $p = 0.0002$; Logical Reasoning RT, $t(75) = 3.73$, $p = 0.0008$; Mathematical Processing RT, $t(75) = 4.61$, $p = 0.0002$; Tracking error, $t(75) = 3.28$, $p < 0.0032$; and, Visual Vigilance hits, $t(75) = 7.19$, $p < 0.0001$.

At 5.5 h post-drug administration (Day 4, 21.00 h), significant performance improvements were found for: Running Memory RT, $t(74) = 6.94$, $p = 0.0002$; Logical Reasoning RT, $t(75) = 5.11$, $p = 0.0002$; Mathematical Processing RT, $t(75) = 2.88$, $p = 0.0106$; Visual Vigilance RT, $t(75) = 3.80$, $p = 0.0003$; and, Visual Vigilance hits, $t(75) = 6.68$, $p < 0.0001$.

Drug Effects on Performance Showing no Sleep Deprivation Deficits

For some tasks, where no performance deficits occurred due to sleep deprivation, there were nonetheless improvements following administration of D-amphetamine, phentermine, caffeine, and/or tyrosine. None showed performance improvements following placebo administration. Again, statistical analyses compared performances at each of the two post-drug test sessions with the pre-drug, 30-h sleep deprivation, baseline test session (Day 4, 13.00 h).

Tyrosine improved performance for two tasks that did not show effects of sleep deprivation, but only at the 5.5 h post-drug session. Stroop task RT improved 42 ms, $t(75) = 3.81$, $p = 0.0006$; and, four-choice serial RT improved 15 ms, $t(75) = 2.36$, $p = 0.0418$.

D-Amphetamine effects were shown for Stroop task as RT improved 39 ms at 1.5 h post-drug, $t(75) = 3.79$, $p = 0.0006$, and an additional 10 ms at 5.5 h post-drug, $t(75) = 5.07$, $p = 0.0002$. Four-choice serial RT improved 19 ms at 1.5 h post-drug, $t(75) = 3.48$, $p = 0.0016$, and 21 ms at 5.5 h post-drug, $t(75) = 3.15$, $p = 0.0048$.

Phentermine improved performance for the same tasks as D-amphetamine, plus one additional task. The significant improvements related to phentermine were for Stroop task as RT improved 32 ms at 1.5 h post-drug, $t(75) = 2.78$, $p = 0.0136$, and 55 ms at 5.5 h post-drug, $t(75) = 5.21$, $p = 0.0002$. Four-choice serial RT improved 18 ms 1.5 h post-drug, $t(75) = 3.07$, $p = 0.006$, and 34 ms at 5.5 h post-drug, $t(75) = 5.67$, $p = 0.0002$. The additional performance effect was for Visual Scanning detection time where detection time improved 2.1 s at 1.5 h post-drug, $t(74) = 3.09$, $p = 0.0056$.

Caffeine also influenced performance for three tasks that did not show deterioration during sleep deprivation. Stroop task RT improved 50 ms at 1.5 h post-drug, $t(75) = 5.35$, $p = 0.0002$, and 45 ms at 5.5 h post-drug, $t(75) = 4.90$, $p = 0.0002$; Four-choice serial RT improved 25 ms at 5.5 h post-drug,

$t(75) = 4.70$, $p = 0.0002$; and, Trails (B) completion time improved 7.4 s at 1.5 h post-drug, $t(75) = 2.62$, $p = 0.02$.

DISCUSSION

Performance deficits due to 30 h of sleep deprivation were found only for some tests included in the battery used in this study. Those tests involving time stress (i.e. performance required speed and accuracy) showed more consistent performance deficits during sleep deprivation than performance measures related to correctness of responses.

D-amphetamine is a potent releaser of catecholamine, which is associated with behavioral arousal and enhanced attention. D-amphetamine has been shown in numerous research studies to reverse cognitive performance deficits due to sleep deprivation (e.g. Newhouse *et al.*, 1989; Newhouse *et al.*, 1992; Caldwell *et al.*, 1995; Pigeau *et al.*, 1995). Newhouse *et al.* (1989) showed that 10 and 20 mg doses of D-amphetamine, administered after 48 h of continuous sleep deprivation, led to performance that returned to baseline levels for accuracy on a sustained attention, machine-paced serial addition and subtraction task. The 20 mg dose enabled subjects to maintain this level of performance for 12 h. Caldwell *et al.* (1995) reported that D-amphetamine facilitated helicopter pilot performance on an aviator simulator after 22, 26 and 34 h of continuous wakefulness.

Because the performance improvements related to D-amphetamine 20 mg are in harmony with previous research (e.g. Newhouse *et al.*, 1992; Caldwell *et al.*, 1995; Pigeau *et al.*, 1995), they can be considered as the effects against which those of the other substances used in this study can be evaluated. In light of this comparison approach, the most notable results of this study are that caffeine and phentermine led to performance improvements that were similar to those of D-amphetamine.

Caffeine has its primary effect via the inhibition of adenosine receptors, with a smaller, secondary effect of enhanced catecholamine release. There is ample evidence that demonstrates the effect of caffeine on various aspects of human behavior (Lieberman, 1992), including sleep deprivation (Hindmarch *et al.*, 2000; Kamimori *et al.*, 2000; Lagarde *et al.*, 2000; Beaumont *et al.*, 2001; De-Valck and Cluydts, 2001; Van Dongen *et al.*, 2001; Wesensten *et al.*, 2002. Caffeine can be effective for overcoming deficits in cognitive performance related to sleep loss (Bonnet and Arand, 1994; Bonnet *et al.*, 1995; Hindmarch *et al.*, 2000; Kamimori *et al.*, 2000; Lagarde *et al.*, 2000; Beaumont *et al.*, 2001; De-Valck and Cluydts, 2001; Van Dongen *et al.*, 2001; Wesensten *et al.*, 2002). Penetar *et al.* (1993) reported that caffeine (150, 300, or 600 mg/70 kg doses) led to elevated levels of alertness after 49 h without sleep for the highest doses, but alertness in this study was assessed only by means of mood ratings.

When caffeine doses of 300 mg/70 kg body weight (the equivalent of two to three cups of coffee) were administered to subjects after 32.5 h without sleep, performance improved on several tasks that involved cognition, attention and motor performance. Tasks that required short-term memory, logical reasoning, mathematical calculations and visual vigilance improved in test sessions that occurred at 1.5 and 5.5 h after caffeine was administered. In addition, improvements in pursuit tracking performance occurred at the 1.5 h test session. The primary benefit to performance derived from caffeine was a decrease in the amount of time subjects required to initiate a response (i.e. response delay time). However, there also was an increase in the number of hits and a reduction in the error for the visual vigilance and pursuit tracking tasks, respectively.

Phentermine is a β-phenethylamine with very low abuse potential that has not been previously investigated as a strategy to help overcome performance deficits due to prolonged sleep deprivation. The results of the present study show that phentermine can be used for this purpose. The effects of phentermine 37.5 mg on sleep-deprived performance mimicked those of D-amphetamine 20 mg. At test sessions conducted 1.5 and 5.5 h after phentermine was administered, performance improved on tasks that required short-term memory, logical reasoning, mathematical calculations, visual vigilance and pursuit tracking. Again, the primary performance benefit was a decrease in the amount of time subjects required to initiate a response, although improvement was also shown in the number of hits and the amount of error for the visual vigilance and pursuit tracking tasks, respectively.

Tyrosine also showed some positive effects for overcoming performance deficits due to prolonged sleep deprivation. However, where improvements in performance were found, they were generally delayed in comparison to the effects found for the other substances. Of the four tasks where performance improved following the administration of tyrosine, only one task (mathematical processing) showed improvement 1.5 h after tyrosine was administered. The other tasks (running memory, logical reasoning, and visual vigilance) showed improvement only at the 5.5 h test session. Again, the performance effect for each of these tasks was a decrease in the amount of time required to initiate a response, although there also was an increase in the number of hits for the visual vigilance task. Given the limited amount of investigation with tyrosine,

these results are encouraging and suggest the need for further investigation.

The present study is consistent with previous research (Lieberman, 1992; Newhouse *et al.*, 1992; Caldwell *et al.*, 1995; Pigeau *et al.*, 1995) showing that D-amphetamine 20 mg and caffeine 150 mg/kg typically enabled sleep-deprived subjects to improve performance. In addition, the present study showed that phentermine 37.5 mg also improved sleep-deprived performance.

Although the effects of tyrosine 300 mg/70 kg were less consistent than the other substances, tyrosine also significantly improved sleep-deprived performance on several tests. This is in part consistent with earlier research (Neri *et al.*, 1995). In that study subjects performed nine iterations of a battery of performance tests for up to 24 h of wakefulness. The tyrosine dose was 150 mg/Kg and the drug was administered after about 18 h of wakefulness and produced significant improvement in deficits in tracking performance for one to three hours and improvement in deficits in running memory for one to four hours. Our study was similar for running memory but not for tracking, perhaps due to the more severe sleep deprivation in our study. Thus the tyrosine effects were sufficiently positive to indicate its potential for use in sleep-deprived situations, especially for responses at 5.5 h from dosing and beyond, and to warrant further study to investigate its use in these situations.

Two questions remain to be addressed. The first concerns the reasons why the various substances investigated led to the improved performance that were found in this study. The other concerns the practical significance of the results of this study. Each substance used in this investigation influences the function of the central nervous system, albeit in slightly different ways. Phentermine and D-amphetamine release and may also block re-uptake of catecholamines, whereas caffeine inhibits adenosine receptors, thus modulating G-protein coupled membrane activity. Tyrosine is a natural precursor for synthesis of catecholamine neurotransmitters dopamine, norepinephrine and epinephrine. As Dinges (1992) pointed out in his review of the effects of sleep deprivation on human performance, attention-related functions such as cognitive processing speed, vigilance and alertness deteriorate to some extent because of sleep loss. In the present study, evidence supporting these types of effects was found to be the basis for the significant deficits in performance associated with 30 h of sleep deprivation. Performance deficits were found for tasks that required short-term memory, logical reasoning, mathematical calculations, visual vigilance, and manual pursuit tracking. That attention/alertness factors led to performance deficits on these tasks is established by the finding that the significant deficits in performance were typically for response delay dependent measures. In addition, these performance deficits were overcome following the administration of doses of D-amphetamine, phentermine, caffeine and tyrosine after more than 32.5 h without sleep. The positive effects of these substances occurred as soon as 1.5 h, and lasted as long as 5.5 h after dose administration.

Most of the performance deficits found in this study involved a lengthening in the amount of time subjects took to initiate a response in a time-stress task. That is, when subjects had to respond accurately and quickly, they chose to maintain the accuracy of their responses even though this required more time to produce a response. Thus, subjects traded-off speed for accuracy. The behavioral benefit of the CNS-activating substances used in this study was that sleep deprived subjects did not have to make this trade-off. And, in the case of the visual vigilance task and manual pursuit tracking, they performed more accurately.

The practical significance of this study is particularly meaningful when the actual amounts of response-delay time are considered. For example, for the logical reasoning task, when subjects were deprived of sleep for 28 h (Day 4 at the 1:00p.m. test session), the response delay increase was almost 0.6 s. Not only is this amount of increase in time statistically significant, it also is significant in terms of its practical application. If individuals are engaged in a time-stress situation in which they must perform a task that involves logical reasoning, a 0.6 s increase in the amount of time required to make a response, even if correct, could be the difference between life and death, depending on the circumstances. What becomes particularly notable is that the doses we tested of D-amphetamine, phentermine and caffeine reduced the response-delay to near-baseline levels. Interestingly, although not statistically compared, caffeine reduced the amount of the response-delay the closest to the pre-sleep deprived baseline for both the post-drug test sessions. Even tyrosine was associated with a reduction in the response-delay time to near baseline levels, but only at the later (5.5 h post-drug) test session.

Finally, the drugs tested in this study improved performance on several tests in sleep-deprived subjects when performance on these tests had not even deteriorated during sleep deprivation. Thus, for short-term use in situations of sleep deprivation, caffeine and phentermine, which have minimal abuse problem, appear to be useful. The value of tyrosine may be limited by its low potency and the amount required for the measured improvements. However, tyrosine clearly appears to have potential to improve performance in sleep deprivation situations.

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