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ORIGINAL INVESTIGATION

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Effects of caffeine, sleep loss, and stress on cognitive performance and mood during U.S. Navy SEAL training

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Abstract *Rationale:* When humans are acutely exposed to multiple stressors, cognitive performance is substantially degraded. Few practical strategies are available to sustain performance under such conditions. *Objective:* This study examined whether moderate doses of caffeine would reduce adverse effects of sleep deprivation and exposure to severe environmental and operational stress on cognitive performance. *Methods:* Volunteers were 68 U.S. Navy Sea-Air-Land (SEAL) trainees, randomly assigned to receive either 100, 200, or 300 mg caffeine or placebo in capsule form after 72 h of sleep deprivation and continuous exposure to other stressors. Cognitive tests administered included scanning visual vigilance, four-choice visual reaction time, a matching-to-sample working memory task and a repeated acquisition test of motor learning and memory. Mood state, marksmanship, and saliva caffeine were also assessed. Testing was conducted 1 and 8 h after treatment. *Results:* Sleep deprivation and environmental stress adversely affected performance and mood. Caffeine, in a dose-dependent manner, mitigated many adverse effects of exposure to multiple stressors. Caffeine (200 and 300 mg) significantly improved visual vigilance, choice reaction time, repeated acquisition, self-reported fatigue and sleepiness with the greatest effects on tests of vigilance, reaction time, and alertness. Marksmanship, a task that requires fine motor coordination and steadiness, was not affected by caffeine. The greatest effects of caffeine were present 1 h post-administration, but significant effects persisted for 8 h. *Conclusions:* Even in the most adverse circumstances, moderate doses of caffeine can improve cognitive function, including vigilance, learning, memory, and mood state. When cognitive performance is critical and must be maintained during exposure to severe stress, administration of caffeine may provide a significant advantage. A dose of 200 mg appears to be optimal under such conditions.

Keywords Stress · Vigilance · Mood · Alertness · Psychomotor performance · Learning · Memory · Stimulant

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Introduction

Caffeine is widely consumed throughout the world in beverages, foods, and as a drug for a variety of reasons, including its stimulant-like effects on mood and cognitive performance (for reviews see Fredholm et al. 1999; Lieberman 2001). Its positive effects on performance, notably sustained vigilance and related cognitive functions, are well documented when it is administered to rested volunteers in the doses found in single servings of foods (Amendola et al. 1998; Clubley et al. 1979; Fine et al. 1994; Lieberman et al. 1987a, 1987b; Smith et al. 1999a, 1999b).

Caffeine, in moderate and high doses, also has been shown to have beneficial effects on cognitive performance when individuals are sleep-deprived (Patat et al. 2000; Penetar et al. 1993; Reyner and Horne 2000). However, few studies have examined the effects of caffeine during exposure to severe, multifactor stress to determine whether it can mitigate the adverse effects of simultaneous exposure to a combination of stressors. Furthermore, the optimal dose to employ under such conditions has not been determined (Akerstedt and Ficca 1997). Military training environments can provide one of the few opportunities to examine the effects of severe, but controlled, multifactor stress on human performance. Therefore we examined the effects of caffeine on

cognitive performance and mood during training of the United States Navy Sea-Air-Land Commandos.

The SEALs are one of the most elite special warfare units in the U.S. Defense Department. Operational SEAL units conduct unconventional warfare and clandestine operations in maritime and riverine environments (Waller 1994). To become a SEAL member an individual must complete a four-part training program lasting about 7–8 months at the Naval Special Warfare Training Center (NSWTC), Naval Amphibious Base, Coronado, California. The training is intense, difficult, and designed to identify individuals who can withstand the adverse effects of a variety of operational stressors, especially exposure to cold water and sustained high levels of intense physical activity, while maintaining high levels of physical and mental function. Due to the rigorous mental and physical challenges of training only about one in four individuals who attempt the course complete it (Waller 1994). One of the most acutely stressful periods of SEAL training is "Hell Week," during which trainees undergo sustained sleep loss in combination with extensive environmental, physical and psychological stress. Most Hell Week activities are conducted on the beach, surf, or in small boats. These are environments in which SEAL members may work when they conduct operations.

During Hell Week trainees are under continuous supervision of trained SEAL instructors and engage in continuous 24– h activities. These include physical and mental challenges, environmental stress, especially cold stress, as well as constant psychological pressure to perform optimally as an individual and part of a small team (Waller 1994). The challenges of Hell Week include a variety of activities such as surf immersion, where students, arms linked, sit in a line so the surf strikes them in the face. This lasts for a period of 10–20 min depending upon water temperature. Boat push-ups are another frequent activity with trainees expected to raise inflatable boats over their heads, and then as a team push them up until their arms are fully extended. The boats contain life vests, paddles, and often a considerable amount of water. Other more traditional forms of physical training such as push-ups and sit-ups are frequently required of trainees by the instructors. Psychological stressors include verbal confrontations with instructors and activities with no-win outcomes (Smoak et al. 1988). During Hell Week trainees only have a few hours to sleep during irregular breaks in training and are often wet and cold. Since actual SEAL operations, including combat, can involve these challenges in combination with life-threatening danger, Hell Week provides an opportunity to determine which trainees have the physical and mental attributes to perform reliably under such conditions. Generally more than one-half the trainees who start Hell Week do not complete it and therefore cannot continue SEAL training. Most withdrawals from training are voluntarily initiated by the trainee, except for medical withdrawals. The training repeatedly pushes trainees to their physical and mental limits so that they will be prepared for the extraordinary challenge of serving in operational SEAL units.

Because caffeine may maintain cognitive performance under conditions of severe stress, we conducted a dose-response study to evaluate its effects during Hell Week of SEAL training. We assessed a variety of behavioral functions, focusing on parameters sensitive to caffeine such as vigilance (Clubley 1979; Fine et al. 1994; Lieberman 1992) and mood (Amendola et al. 1998). We measured salivary caffeine and self-reported side effects. In addition, we utilized a simulated marksmanship task to provide information on a complex behavior that requires fine motor control and steadiness for optimal performance (Kruse et al. 1986; Zatsiorsky and Aktov 1990). Caffeine has been anecdotally reported to interfere with these psychomotor functions, although the literature suggests that caffeine does not adversely affect fine motor control (Lieberman et al. 1987b; Patat et al. 2000).

Methods and materials

Subjects

A total of 68 male SEAL trainees participated in this study out of 90 who initially volunteered. All of those who did not participate were no longer in Hell Week when testing was conducted. No volunteer dropped out because of our testing. Mean age of the volunteers was 23.9±3.0 years. Their mean weight was 77.3±8 kg, and they had served on average 3 years in the military. There were no differences in any demographic characteristic between treatment groups including age, weight, and service history. Prior to Hell Week all subjects were briefed on the study and gave their written informed consent. They were free to withdraw from the study at any time without penalty. The study was approved by the appropriate institutional review boards.

During Hell Week trainees were not permitted to consume coffee or other beverages containing caffeine, to smoke or to have any personal food, which is consistent with standard SEAL training policy, although food intake was not restricted. Trainees received four regular meals each day, including supplemental rations, due to their high energy expenditure, which has been estimated to be 24 MJ/day (DeBolt et al. 1998).

General procedures

This double-blind, placebo-controlled study was conducted at the NSWTC on the coast just southwest of San Diego, California. Caffeine in doses of 100, 200, or 300 mg or identical placebo capsules containing cellulose, were administered to volunteers who were randomly assigned to one of the treatments. The number of capsules taken by all groups was identical. Testing was conducted during the Hell Week phase of SEAL Training (Smoak et al. 1988; Waller 1994). During the week preceding Hell Week demographic information was obtained from subjects, training on the individual test procedures was conducted, and baseline behavioral data were collected. Hell Week began on Sunday night, and the following Wednesday night at 21:30 hours caffeine or placebo was administered. Volunteers had only one brief opportunity to sleep (for 90 min on Wednesday) about 15 h prior to administration of the treatments. Therefore subjects were almost totally sleep-deprived for 72 h prior to administration of the test substances.

For 1 h after treatment volunteers continued regular training on the beach at the NSWTC. At 22:30 h volunteers reported to a nearby classroom where tests were administered for 1 h. After testing was completed, volunteers ate a meal served at a mess hall

during which they were monitored to ensure they did not consume any caffeine-containing beverages or foods. They then resumed physically demanding training, including running, lifting, paddling inflatable boats, swimming, and calisthenics. About 8 h after treatment they returned to the classroom, repeated the testing procedures, and completed a posttest questionnaire. Testing was conducted 1 and 8 h after caffeine administration because caffeine's effects are near maximal 1 h after administration and should dissipate by 8 h post-administration (Fine et al. 1994).

Saliva sampling procedures

Saliva was collected to assess pretest caffeine consumption and changes in caffeine levels following treatment. Saliva caffeine levels are highly correlated (r=0.98) with plasma caffeine concentration (Alkaysi et al. 1988). Samples were taken: (a) prior to Hell Week, (b) immediately prior to caffeine/placebo ingestion, (c) 1 h after treatment, and (d) 8 h after treatment. Volunteers provided approximately 10 ml saliva by chewing on a cotton wad, which they deposited in a special centrifuge tube (Sarstedt; Newton, N.C., USA). The samples were frozen and shipped to the Pennington Biomedical Research Center, Baton Rouge, Louisiana, for analysis. Samples were analyzed on the Beckman Synchron CX5 using EMIT reagents for caffeine (Dade-Behring Diagnostics, Deerfield, Ill., USA). The assay is based on competition for antibody binding sites between caffeine in the sample, and caffeine labeled with the enzyme glucose-6-phosphate dehydrogenase.

Cognitive, mood, and marksmanship testing procedures

Four cognitive tests were administered on laptop computers: scanning visual vigilance, four-choice visual reaction time, a matching-to-sample test, and a repeated acquisition test. Each test was administered during a baseline session and 1 and 8 h after treatment. Prior to Hell Week subjects participated in several practice sessions to become familiar with the tests.

Scanning visual vigilance test

This test required the volunteer to detect a faint stimulus that appeared randomly on the screen of a laptop computer for 2 s (Fine et al. 1994; Lieberman et al. 1998). On average, presentation of the stimulus occurred once per minute. Upon detection of the stimulus the volunteer pressed the space bar on the keyboard as quickly as possible. The computer recorded whether each stimulus was detected, as well as response time for correct detections. Responses made before or after stimulus occurrence were recorded as false alarms. Each session lasted 15 min. This test is sensitive to the beneficial effects of caffeine on rested volunteers (Fine et al. 1994).

Four-choice visual reaction time test

Four-choice visual reaction time was assessed by presenting a series of visual stimuli at one of four spatial locations on the computer screen (Dollins et al. 1993). Subjects indicated the correct spatial location of each stimulus by pressing one of four adjacent keys on the keyboard. Dependent measures included correct responses and incorrect responses (hitting the wrong key), response latency for each trial, premature errors (responding before presentation of the stimulus), and time-out errors (response latency longer than 1 s). In total 250 trials were administered. This test is sensitive to sleep deprivation, effects of caffeine in rested subjects (Lieberman et al. 1987b), and a variety of other factors (Dinges 1992; Lieberman et al. 1996).

Matching-to-sample test

This test assesses short-term spatial working memory and pattern recognition (Ahlers et al. 1994; Shurtleff et al. 1994). The volunteer responded by pressing the down arrow key when the word "ready" appeared on the screen of the computer. An 8×8 matrix of red and green blocks in a checkerboard pattern was presented for 4 s and then a variable length interval of either 1 or 15 s occurred, during which the screen was blank (except that the word "delay" appeared at the bottom). After the delay two matrices were presented, one on the left and one on the right; one was the original sample matrix, and the other was a matrix with the color sequence of two of the squares reversed. The volunteer pressed either the left or right arrow key, responding to the location he believed matched the original sample matrix. The task consisted of 20 trials in a random sequence, 10 at each delay. If a response was not made in 15 s, the trial was terminated, and a time-out error was recorded. Correct response latency was also recorded. This test was included because it has previously been shown to be sensitive to the effects of cold stress and dietary interventions on cognitive performance (Ahlers et al. 1994; Shurtleff et al. 1994).

Repeated acquisition test

This test assesses motor learning and short-term memory. The task required the volunteer to learn a sequence of key presses on a computer. As the task proceeded, a visual stimulus on the computer screen was modified based on the whether the subject made a correct or incorrect key press. Specifically, the volunteer learns a random sequence of 12 key presses using the four arrow keys of the laptop computer. The outline of a rectangle was presented on the screen at the beginning of a trial. Each correct response filled in a portion (1/12th) of the rectangle from left to right with a solid square. A key press was considered to be correct when the subject made a response, which corresponded to the predetermined correct answer for that location (sequence) in the bar. Each incorrect response blanked the screen for 0.5 s, and when the rectangle reappeared, the volunteer was at the same point in the sequence as before the error. The volunteer had to learn the correct sequence by trial and error. When a sequence was correct, the rectangle was filled, the screen blanked and another empty rectangle reappeared for the next trial. A session ended when the volunteer completed 15 correct sequences (15 trials). Incorrect responses and time to complete each trial were recorded. This test was included because it has previously been shown to be sensitive to the effects of cold stress and dietary interventions on higher level cognitive performance (Ahlers et al. 1994).

Profile of Mood States questionnaire

The Profile of Mood States (POMS) is an inventory of mood states (McNair et al. 1971). The volunteers rated 65 mood-related adjectives on a five-point scale in response to the question, "How are you feeling right now?" The adjectives factor into six mood subscales: tension, depression, anger, vigor, fatigue, and confusion (McNair et al. 1971). Four subscales (tension, depression, vigor, and fatigue) are sensitive to caffeine in the dose range employed in this study (Amendola et al. 1998; Fine et al. 1994; Lieberman et al. 1987a).

Stanford Sleepiness Scale

The Stanford Sleepiness Scale (SSS) is a seven-item, self-report scale of an individual's state of sleepiness (Hoddes et al. 1973) sensitive to effects of caffeine (Lieberman et al. 1987a; Patat et al. 2000).

Marksmanship procedure

Rifle marksmanship was assessed with the Noptel ST-1000 laser marksmanship system (Oulu, Finland) attached to a disabled AK-47 rifle. The simulator consists of a laser transmitter, an optical glass and laser-sensitive receiver with a paper aiming target and a personal computer (Tharion et al. 1992). Marksmanship parameters assessed were the distance from center of mass, shot group tightness, number of missed targets, and sighting time (Tharion et al. 1992). During testing, volunteers lay in the prone firing position and used sandbags to support the rifle. Following a "ready signal" and an interval of 1–10 s (randomly varied), a red light emitting diode was illuminated indicating the subject could start shooting. Volunteers then fired at the target as quickly and accurately as possible. A total of eight shots were fired at each test session.

Posttest questionnaire

A posttest questionnaire was administered to determine whether volunteers believed they had been given caffeine, if it seemed to be beneficial, and if they experienced any side effects of caffeine.

Statistical analyses

Descriptive statistics were computed to assess central tendency and level of dispersion at baseline and 1 and 8 h after treatment. To determine the effects of Hell Week compared to baseline on performance and mood, repeated measures, within-subjects analyses of variance (ANOVAs), with test session as the grouping factor, were conducted. To isolate the effects of caffeine difference-from-baseline test scores were derived and one-way ANOVAs for the 1- and 8-h test sessions were performed. In addition, all possible post hoc contrasts between the different caffeine doses and placebo were conducted using Duncan's multiple comparison tests. To assess dose-response relationships across caffeine doses, preplanned orthogonal component analyses were performed on change from baseline scores for each cognitive and mood variable. Frequency tables for side effects were obtained by caffeine group, and a χ^2 analysis was used to assess differences in observed frequencies between groups.

Results

Effects of sleep deprivation and operational stress on performance and mood

Virtually all cognitive and mood parameters assessed were substantially degraded at both test sessions conducted during Hell Week compared to the pre-Hell Week baseline session. Visual vigilance measures at both Hell Week test sessions were all significantly impaired compared to baseline measures collected the week preceding Hell Week. For the pooled data for all treatment groups, hits on the vigilance task decreased ($F_{2,108}$=98.12, P=0.0001). At the first Hell Week session hits on the vigilance task decreased from a mean of 18 (90% correct) at baseline to 10.6 (53% correct). Reaction time on the vigilance task at the first Hell Week session increased from 0.9 to 1.2 s ($F_{2,108}$=10.46, P=0.0001). False alarms increased 181% from baseline to the first test during Hell Week and were also degraded 8 h post-treatment ($F_{2,108}$=5.10, P=0.0077). Four-choice visual reaction time number correct ($F_{2,110}$=15.76, P=0.0001), latency ($F_{2,110}$=60.57, P=0.0001), premature errors ($F_{2,110}$=3.72, P=0.0274), and time-out errors ($F_{2,110}$=16.36, P=0.0001) were also impaired during both Hell Week tests compared to baseline.

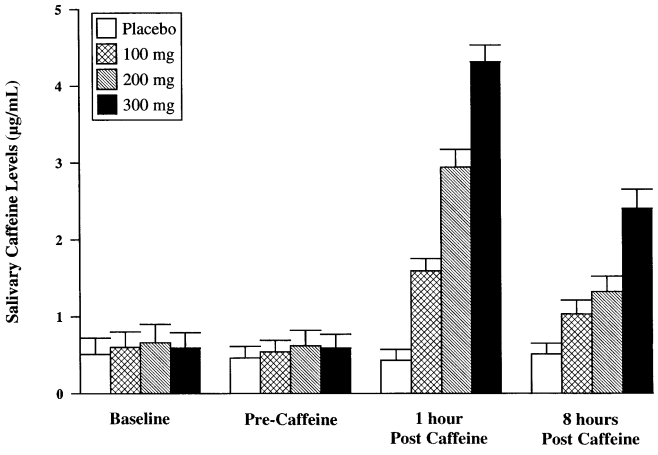

Fig. 1 Mean (±SEM) saliva caffeine concentration preceding Hell Week, immediately prior to caffeine administration and 1 h and 8 h after administration of caffeine

On all measures of the matching-to-sample task, performance was significantly impaired during both Hell Week test sessions compared to baseline. Correct responses decreased ($F_{2,124}$=11.20, P=0.0001), reaction time increased ($F_{2,124}$=21.48, P=0.0001) and time-out errors increased ($F_{2,124}$=11.79, P=0.0001). Performance on the repeated acquisition test also showed impairments during both Hell Week test sessions with incorrect responses ($F_{2,120}$=21.62, P=0.0001), as well as time-to-completion increasing ($F_{2,120}$=37.14, P=0.0001), compared to the pre-Hell Week. Mood state assessed by the POMS and SSS deteriorated substantially during Hell Week compared to baseline measures. Increases in depression ($F_{2,120}$=52.72, P=0.0001), fatigue ($F_{2,120}$=110.97, P=0.0001), confusion ($F_{2,120}$=85.25, P=0.0001; POMS) and sleepiness ($F_{2,114}$=125.85, P=0.0001; SSS) were observed. Various aspects of marksmanship were also impaired during Hell Week compared to baseline: distance from center of mass ($F_{2,116}$=4.47, P=0.0135), shot group tightness ($F_{2,116}$=5.05, P=0.0079), sighting time ($F_{2,116}$=41.14, P=0.0001), and number of missed targets ($F_{2,116}$=4.73, P=0.0106).

Performance and mood state, measured prior to Hell Week, did not predict the likelihood of a volunteer successfully completing Hell Week training.

Saliva caffeine

There were dose-dependent changes in caffeine saliva levels following caffeine administration (Fig. 1). Significant 1 h post-ingestion differences existed between all dosing groups ($F_{3,57}$=34.516, P=0.0001), with caffeine levels increasing as dose increased. All post hoc com-

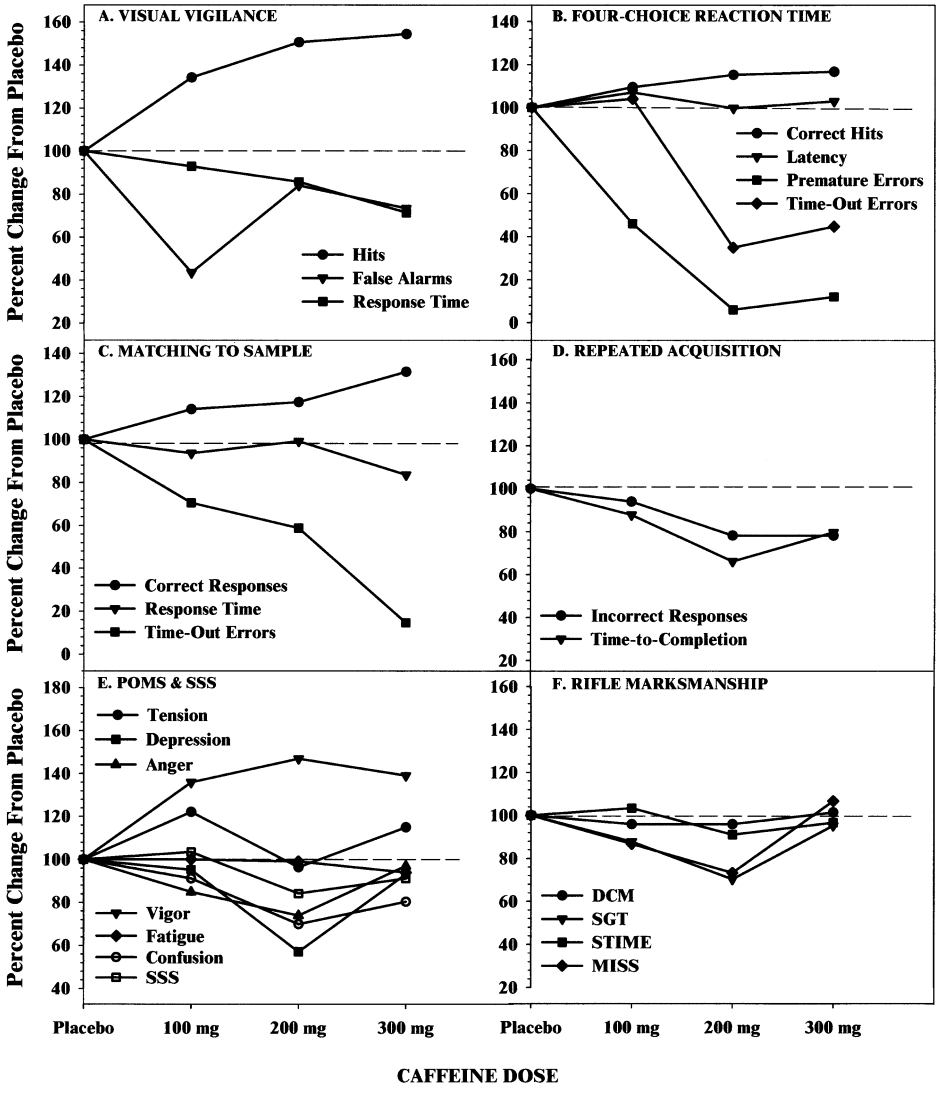

Fig. 2A–F Percentage change in performance and mood following varying doses of caffeine compared to placebo treatment 1 h after caffeine administration. The behavioral data are presented in this format solely for visual comparison; no statistical tests were performed on the transformed data. **A** Percentage change from placebo on measures of visual vigilance. **B** Percentage change from placebo on the four-choice visual reaction time test. **C** Percentage change from placebo on the matching-to-sample test. **D** Percentage change on the repeated acquisition test. **E** Percentage change from placebo on the POMS and SSS. **F** Percentage change from placebo on measures of rifle marksmanship

parisons were significant ($P<0.05$). By 8 h post-treatment, significant differences were still present ($F_{3,49}=34.49$, $P=0.0001$). Post hoc tests between placebo and the 200- and 300-mg dose levels were significant ($P<0.05$) but not those for the placebo verses 100 mg comparison. No significant difference between baseline (4 days prior to Hell Week) and pre-caffeine administration levels during Hell Week was observed (paired t test: $t_{64}=0.478$, $P=0.63$). Therefore typical dietary levels of caffeine intake by the subjects were not high and did not decline during Hell Week; hence any effects of caffeine withdrawal would have been modest in these volunteers.

Caffeine effects on performance and mood

Mean (±SEM) scores and results of statistical tests from all performance and mood dependent variables are presented in Tables 1, 2, 3, 4. To permit visual examination and comparison at the test session during which caffeine exerted its maximal effects (the 1-h post-caffeine test session), the mean value for every behavioral parameter at each dose of caffeine was converted to proportional change from placebo, and the results are plotted in Fig. 2. Percentages were used to normalize across all test parameters so that the direction and magnitude of caffeine's effects on each parameter at every dose of caffeine would be apparent on inspection. This transformation was conducted solely to permit visual examination, and no statistical tests were performed on the transformed values.

Visual vigilance

Caffeine produced significant beneficial, dose-related effects including an increase in number of correct responses ($F_{3,54}=2.84$, $P=0.0464$) and a decrease in response time ($F_{3,54}=2.93$, $P=0.0418$) for visual vigilance difference scores 1 h post-administration (Table 1). As the dose increased, more targets were detected ($P=0.003$), and response time was shorter ($P=0.003$), as demonstrated

Table 1 Effect of caffeine on performance 1 h after administration

Visual vigilance	Placebo (n=15)	100 mg caffeine (n=16)	200 mg caffeine (n=14)	300 mg caffeine (n=13)	ANOVA
Hits: maximum=20	7.9±1.4[a]	10.6±1.5[a,b]	11.9±1.7[a,b]	12.2±1.4[b]	Main effect: P<0.050, linear: P=0.003
Total false alarms	65.7±38.3	28.6±14.8	55.2±51.0	48.2±36.0	NS
Response time	1.4±0.2[a]	1.3±0.1[a]	1.2±0.1[a,b]	1±0.1[b]	Main effect: P<0.050, linear: P=0.003
Four-choice visual reaction time	(n=14)	(n=15)	(n=15)	(n=15)	
Correct hits: total=250	201.2±15.8[a]	220.3±10.3[a,b]	231.7±5.7[b]	235±3.9[b]	Main effect: P<0.050, linear: P=0.003
Latency: correct hit (ms)	626.0±23.2	669.6±32.5	624.4±30.3	644.2±32.8	Linear: P=0.057
Premature errors (total)	5.0±3.2	2.3±0.8	0.3±0.1	0.6±0.3	Linear: P=0.022
Time-out errors (total)	15.2±4.2	15.8±6.3	5.3±3.2	6.5±3.1	Linear: P=0.044
Matching-to-sample	(n=17)	(n=17)	(n=17)	(n=16)	
Correct responses (total)	9.2±0.9	10.5±0.8	10.8±1.0	12.1±0.8	Cubic: P=0.0890
Response time (s)	6.7±0.8	6.3±0.6	6.7±0.6	5.6±0.4	NS
Time-out errors (total)	3.4±1.3	2.4±0.9	2.0±0.8	0.5±0.3	Linear: P=0.023
Repeated acquisition	(n=17)	(n=16)	(n=17)	(n=16)	
Incorrect responses	13.3±1.5	12.5±1.1	10.4±1.5	10.4±1.5	Linear: P=0.0169
Time-to-completion (s)	43.3±4.8[a]	38.0±4.4[a,b]	28.6±3.0[b]	34.5±4.9[a,b]	Main effect: P=0.02, linear: P=0.011

[a,b]Different superscripts indicate drug groups are different from one another at P<0.05 (Duncan's test)

Table 2 Effect of caffeine on performance 8 h after administration

Visual vigilance	Placebo (n=15)	100 mg caffeine (n=16)	200 mg caffeine (n=14)	300 mg caffeine (n=13)	Significance
Hits: maximum=20	7.5±1.34[a]	7.2±1.25[a]	10.6±1.4[b]	9.8±1.1[a,b]	Main effect: P<0.050, linear: P=0.0075
Total false alarms	26.1±9.7	175.3±102.1	270.9±165.0	127.3±53.6	NS
Response time	1.3±0.1	1.7±:35	1.2±0.1	1.3±0.08	NS
Four-choice visual reaction time	(n=14)	(n=15)	(n=15)	(n=15)	
Correct hits: total=250	221.4±7.67	217.5±8.1	234.2±2.4	233.5±3.7	NS
Latency: correct hit (ms)	620.4±23.6	645.5±23.0	670.3±33.2	639.7±25.1	Linear: P=0.0764
Premature errors (total)	2.6±1.39	1.9±1.2	0.7±0.2	0.9±0.6	NS
Time-out errors (total)	13.7±4.12	13.7±5.5	15.6±3.82	10.2±4.1	NS
Matching-to-sample	(n=16)	(n=17)	(n=17)	(n=16)	
Correct responses (total)	10.8±0.73	10.5±0.7	11.4±0.7	10.4±0.6	NS
Response time (s)	5.1±0.35	5.9±0.6	6.1±0.4	5.7±0.45	Linear: P=0.0559
Time-out errors (total)	0.7±0.23	1.5±0.6	1.2±0.36	1.3±0.5	NS
Repeated acquisition	(n=16)	(n=16)	(n=17)	(n=16)	
Incorrect responses	14.3±1.15	14.2±1.0	11.9±1.4	12.5±1.4	NS
Time-to-completion (s)	43.5±1.93[a]	41.0±4.25[a,b]	31.1±2.2[b]	33.8±3.7[b]	Main effect: P=0.030

[a,b]Different superscripts indicate drug groups are different from one another at P<0.05 (Duncan's test)

by significant linear factors on the orthogonal ANOVA comparisons for each parameter. On post hoc testing the number of correct responses made by the 300-mg group was significantly greater than placebo (P<0.05). Response time for the 300-mg group was faster than the placebo or 100-mg groups (P<0.05). At 8 h post-administration (Table 2), a significant effect of caffeine for the correct hit parameter was still present ($F_{3,54}$=2.94, P=0.0411) with the 300-mg group having a smaller decrement (P<0.05) from baseline than either the placebo or 100-mg group on post hoc testing. There was a significant linear, dose-related orthogonal component associated with this effect (P=0.008).

Four-choice visual reaction time test

A significant difference was observed in change from baseline between drug groups for total correct responses (Table 1) ($F_{3,55}$=2.79, P=0.0489), with the 300 and 200-mg groups showing better performance (P<0.05) compared to placebo at 1 h on post hoc testing. A significant linear orthogonal component indicates that these were dose-related effects (P=0.003). The orthogonal components analyses demonstrated there were also linear, dose-related reductions in premature errors (P=0.022) and time out errors (P=0.044) on this test. On average a tenfold decrease in premature errors occurred between placebo group (mean 5.0 errors) and both the 200- and 300-mg groups. Similarly, over twice the number of time-out

Table 3 Profile of Mood States (*POMS*) and Stanford Sleepiness Scale (*SSS*) Score measures by level of caffeine 1 h after administration

POMS	Placebo (*n*=15)	100 mg caffeine (*n*=17)	200 mg caffeine (*n*=17)	300 mg caffeine (*n*=17)	Significance
Tension-anxiety	14.0±1.4	17.1±1.4	13.5±0.95	16.1±1.8	NS
Depression-dejection	14.7±2.1	14.0±2.7	8.4±1.4	13.7±2.3	Linear: *P*=0.060
Anger-hostility	16.5±1.9	14.0±2.5	12.2±1.9	16.0±2.0	NS
Vigor-activity	6.4±1.24	8.7±1.3	9.4±1.4	8.9±1.5	Linear: *P*=0.019
Fatigue-inertia	21.6±1.03[a]	21.6±1.33[a]	21.4±1.1[a]	20.3±1.1[b]	Main effect: *P*=0.03, linear: *P*=0.006
Confusion-bewilderment	14.3±6.1	13.1±1.4	10.0±1.0	11.5±1.5	Linear: *P*=0.013
SSS	5.7±0.2[a]	5.9±0.2[a]	4.8±0.4[b]	5.2±0.34[b]	Main effect: *P*=0.03, linear: *P*=0.002

[a,b]Different superscripts indicate drug groups are different from one another at $P<0.05$ (Duncan's test)

Table 4 Profile of Mood States (*POMS*) and Stanford Sleepiness Scale (*SSS*) Score measures by level of caffeine 8 h after administration

POMS	Placebo (*n*=15)	100 mg caffeine (*n*=17)	200 mg caffeine (*n*=17)	300 mg caffeine (*n*=15)	Significance
Tension-anxiety	11.8±1.24	16.1±1.5	11.3±0.97	13.0±1.8	NS
Depression-dejection	10.3±1.8	10.2±1.7	8.1±1.24	13.1±3.0	NS
Anger-hostility	13.2±2.4	12.6±2.0	9.4±1.55	13.1±2.3	NS
Vigor-activity	7.3±1.3	8.6±1.1	6.5±1.24	7.9±1.9	Cubic: *P*=0.084
Fatigue-inertia	20.7±1.2	21.0±1.2	20.4±1.2	19.1±1.9	Linear: *P*=0.009
Confusion-bewilderment	12.7±0.9	12.5±1.2	11.5±1.1	12.7±1.6	NS
SSS	5.9±0.2[a]	6.2±0.15[a]	5.1±0.36[b]	5.9±0.4[a]	Main effect: *P*<0.05, linear: *P*=0.016

[a,b]Different superscripts indicate drug groups are different from one another at $P<0.05$ (Duncan's test)

errors occurred in the placebo and 100-mg groups compared to both the 200- and 300-mg groups (Table 1). No effects of caffeine on this test were detected at the 8 h testing session.

Matching-to-sample

No significant effects were present on the overall ANOVAs conducted on each parameter. However, the orthogonal components analyses detected a linear, dose-related effect of caffeine ($P=0.023$) at the first post-caffeine test session for time out errors. There were no other statistically significant effects of caffeine.

Repeated acquisition

There was a significant improvement in time-to-completion in this test 1 h after administration (Table 1) due to caffeine ($F_{3,62}=3.54$, $P=0.019$). Subjects receiving the 200-mg dose had the lowest time-to-completion on the task compared to placebo ($P<0.01$ on post hoc testing). There was also a dose-related, linear component present on the orthogonal components analysis ($P=0.011$). In addition, 1 h after administration the number of incorrect responses was lowest in the 200- and 300-mg groups. The orthogonal components ANOVAs confirmed this dose-related effect, as the linear component was significant ($P=0.017$).

At 8 h post-treatment the time-to-completion parameter still showed a significant dose effect ($F_{3,61}=3.43$, $P=0.0225$) (Table 2). Both the 200- and 300-mg caffeine doses had lower times-to-completion than placebo ($P<0.05$). The number of incorrect responses did not differ significantly between groups, although individuals who received the two highest doses performed best.

Profile of Mood States and Stanford Sleepiness Scale

At 1 h post-treatment caffeine lowered the fatigue subscale of the POMS ($F_{3,60}=3.52$, $P=0.0202$), with fatigue reduced in the 300-mg group compared to placebo ($P<0.05$ on post hoc testing; Table 3, Fig. 2). Significant linear ($P=0.006$) and cubic orthogonal components ($P=0.043$) were present. This effect was still present 8 h after caffeine administration ($F_{3,60}=2.93$, $P=0.0409$; Table 4), with the 300-mg dose producing lower fatigue on post hoc testing ($P<0.05$). A linear, dose-related orthogonal component was present as well ($P=0.009$). In addition, 1 h after caffeine ingestion the subjects receiving the 200-mg dose displayed the lowest levels of tension, depression, anger, and confusion, and the highest level of vigor, although these differences were not significantly different (Fig. 2, Table 3).

A dose-response effect for caffeine was observed for the results of the SSS (Fig. 2). At the first post-treatment session, subjects reported they were less sleepy ($F_{3,57}=3.21$, $P<0.03$; Table 3). The 300-mg group showed the smallest increase in sleepiness from baseline, and the placebo group showed the largest increase. The 200- and 300-mg groups' levels were lower than those of the other

Table 5 Percentage of each performance and mood decrement induced by Hell Week training in placebo-treated volunteers that was mitigated by each dose of caffeine 1 h after administration

	100 mg caffeine	200 mg caffeine	300 mg caffeine
Visual vigilance			
Hits	25	38	42
False alarms	77	21	36
Response time	20	40	80
Four-choice visual reaction time			
Correct hits	45	73	81
Latency: correct hits	None	2	None
Premature errors	56	98	88
Time-out errors	None	67	59
Matching-to-sample			
Correct responses	37	46	83
Response time	18	None	50
Time-out errors	31	44	91
Repeated acquisition			
Incorrect responses	20	73	73
Time-to-completion	25	67	41
Marksmanship			
Distance center of mass	23	23	None
Shot group tightness	19	47	9
Sighting time	None	23	17
Misses	22	44	11
Profile of Mood States			
Tension	None	None	None
Depression	7	62	10
Anger	28	48	10
Vigor	36	47	39
Fatigue	None	2	12
Confusion	14	50	33
Stanford Sleepiness Scale	8	35	19

two groups ($P<0.05$ on post hoc testing). There were linear, dose-related effects present after 1 h ($P=0.002$) and 8 h ($P=0.02$), as demonstrated by the orthogonal component tests (Tables 3, 4).

Rifle marksmanship

There were no significant effects of caffeine on any marksmanship parameter.

Posttest questionnaire

Fifty-one percent of volunteers who received caffeine correctly identified it as the treatment and 75% of those who received placebo correctly identified it as their treatment, suggesting that placebo-treated subjects were more likely to correctly identify their treatment condition ($\chi^2=4.02$, $P<0.05$). When asked whether the treatment improved their performance, more individuals who received caffeine, especially the 200-mg dose, indicated it was beneficial than those receiving placebo ($\chi^2=18.37$, $P<0.05$).

There were no significant differences between caffeine and placebo groups on the number of subjective side effects reported. Of the 47 individuals receiving caffeine 15% reported some negative side effects while 6% of those receiving placebo reported side effects. Symptoms reported by caffeine-treated subjects included: nervousness ($n=4$), blurry vision ($n=4$), dizziness ($n=3$), nausea ($n=2$), tiredness/felt a crash ($n=2$), clammy mouth ($n=1$), weak muscles ($n=1$), and felt "flush in the face" ($n=1$).

Discussion

Hell Week of U.S. Navy SEAL training provided a unique opportunity to evaluate the effects of caffeine on individuals exposed to an extraordinarily stressful, but structured, series of physical and cognitive challenges. Sleep loss and exposure to the other stressors of Hell Week resulted in a profound degradation in all aspects of cognitive function assessed. Caffeine mitigated many of these adverse effects (Table 5), improving performance and mood in a dose-related manner. Statistically significant main effects of caffeine were observed on tests of vigilance and choice reaction time, as well as a more complex test of learning and memory, with the most robust effects detected by tests of alertness-related parameters.

Vigilance

Performance on the scanning visual vigilance test was significantly improved by caffeine. Both the number of targets detected and response time measures showed a dose-dependent response pattern, with the largest decrements in the placebo group and the smallest in the 300-mg group. However, in no instance was there a statistically significant advantage of 300 mg compared to 200 mg when a direct comparison was made in the post hoc tests.

Appropriately designed vigilance tests are among the most sensitive measures of caffeine's behavioral effects in rested and sleep-deprived volunteers (Amendola et al. 1998; Bonnet and Arand 1994; Lieberman et al. 1987a, 1987b;). In individuals who are not sleep-deprived, auditory and visual vigilance detection rates are improved by administration of caffeine in doses of 32–256 mg (Amendola et al. 1998; Baker and Theologus 1972; Childs 1978; Fine et al. 1994; Lieberman et al. 1987a, 1987b; Johnson and Merullo 2000). However, in individuals who regularly consume little or no caffeine, higher doses (400 mg) may have a detrimental effect (Childs 1978).

Maintenance of vigilance is essential for numerous critical activities such as vehicle operation, equipment and communication monitoring and sentry duty. When engaged in such activities, failure to detect an infrequent, but important stimulus can be critical (Mitler 1988). The beneficial effects of caffeine may be useful in any situation where sleep deprivation and environmental stressors degrade cognitive function. For example, conducting emergency operations in which environmental stress is substantial, such as disaster relief and forest firefighting, may lead to situations in which adequate rest cannot be obtained. Under such circumstances caffeine in moderate doses may partially restore cognitive function, thereby improving work performance and preventing accidents and injuries. Although this study was conducted during very high levels of stress exposure, the finding should apply to less stressful situations as well. Other studies with similar doses of caffeine demonstrate that it has beneficial effects on vigilance in rested, nonstressed volunteers, as well individuals who have been sleep-deprived, but not exposed to environmental and operational stress (Beaumont et al. 2001; Lieberman et al. 1987a, 1987b).

It should be noted that we did not assess performance of military activities during Hell Week training, rather we employed computer-based, cognitive tasks and our testing sessions may have been perceived by the trainees as a welcome interruption of Hell Week activities. Therefore this study should not be interpreted as conclusively demonstrating that caffeine enhances performance of real-world tasks during highly stressful activities. Additional studies, which actually measure operational performance, should be conducted to address this issue.

Other cognitive tests

Caffeine, in a dose dependent manner, significantly improved performance on the four-choice visual reaction time test 1 h after administration. These results are consistent with previous work on the beneficial effects of caffeine on reaction time tasks (Jacobson and Edgley 1987; Kamimori et al. 2000; Lieberman et al. 1987b; Roache and Griffiths 1987; Smith et al. 1999b).

The effects of caffeine on the matching-to-sample test were statistically less robust than its effects on the other computer-based cognitive tests administered. In a previous study caffeine in doses up to 600 mg did not reduce the adverse effects of 48–64.5 h of sleep deprivation on matching-to-sample performance (Penetar et al. 1994). Therefore this test of working memory is not especially sensitive to the effects of caffeine during sleep deprivation and exposure to stressors.

In the repeated acquisition task caffeine significantly improved time-to-completion 1 h after administration (200 mg) as well as 8 h later (200 and 300 mg). This test requires that subjects learn a complex sequence of motor responses, placing a substantial demand on ability to consolidate new information and to sustain attention for repeated administrations of the test (Ahlers et al. 1994). In rested volunteers caffeine appears to improve performance on tasks that require sustained attention (Meiselman and Lieberman 1994) rather than higher cognitive functions (Amendola et al. 1998; Bättig et al. 1984). The improvements in performance observed in this test may therefore be attributable to improved ability to maintain attention rather than direct effects on working memory. This is consistent with the modest effect caffeine had on the matching-to-sample test, which also requires use of working memory.

Mood state, rifle marksmanship, and side effects

Caffeine administration (300 mg) resulted in significantly smaller increases in fatigue scores on the POMS subscale than placebo both 1 and 8 h after administration. Similarly, sleepiness assessed by the SSS was significantly reduced by 200 and 300 mg caffeine 1 h later. No other mood states differed significantly as a result of caffeine administration, including the anxiety subscale of the POMS. Caffeine's effects on mood state are consistent with its effects on cognitive performance. Penetar et al. (1993) found that fatigue decreased and vigor increased when caffeine was administered in doses of 150, 300, and 600 mg to sleep-deprived individuals.

Sleep deprivation, in combination with other stressors, caused a significant decrease in marksmanship accuracy and an increase in time to sight the target. These adverse effects were not mitigated by caffeine. However, while not statistically significant, caffeine tended to improve performance on several aspects of marksmanship (Fig. 2). Concern that muscle tremor associated with caffeine use (Loke et al. 1985; Svensson et al. 1980) might disrupt

shooting accuracy was not supported, at least when the shooting is done in the prone position as in this study. Psychomotor components of shooting accuracy include steadiness of arm-hand muscles (Kruse et al. 1986; Zatsiorsky and Aktov 1990) and overall body stability (Niinimaa and McAvoy 1983). There was no significant increase in self-reported side effects due to caffeine administration at the doses that we employed; however, at higher doses adverse effects have been noted (Kaplan et al. 1997).

Behavioral effects of caffeine and its mechanism of action

The most robust effects of caffeine in this study were on behavioral tasks or mood states associated with alertness and attention such as visual vigilance, choice reaction time, and fatigue (POMS). In rested individuals caffeine's effects are clearly associated with these functions, as opposed to tasks that require complex information processing, such as memory or reasoning (Amendola et al. 1998; Bättig et al. 1984; Lieberman et al. 1987b). While several studies, in addition to this one, have found that complex tests of cognitive function are improved by caffeine in sleep-deprived volunteers (Beaumont et al. 2001; Penetar et al. 1993), these effects may be secondary to caffeine's effects on alertness and attention. When an individual is engaged in complex cognitive tasks, inability to maintain attention could well cause performance to deteriorate. Such an interpretation is consistent with caffeine's mechanism of action in the CNS and may be the most parsimonious explanation for why caffeine's effects on higher cognitive functions are only observed when individuals are sleep-deprived.

It is widely agreed that caffeine's effects on the brain, when it is administered in doses commonly consumed by humans, are mediated by two classes of adenosine receptors (A_1 and A_{2A}). Caffeine binds to these receptors and blocks the action of agonists on them (for a recent review see Fredholm et al. 1999). These receptors, especially the A_1 class, are closely associated with regulation of alertness. Mesopontine cholinergic neurons are associated with regulation of arousal level and are under tonic A_1 receptor control (Basheer et al. 2000; Portas et al. 1997). Adenosine A_1 agonists, when delivered directly to the basal forebrain, inhibit neurons associated with maintaining wakefulness and A_1 antagonists, including xanthines, increase the activity of these neurons (Basheer et al. 2000). It has been suggested that this region is a site where caffeine exerts its effects on arousal level by acting to block the inhibitory effects of endogenous adenosine (Rainnie et al. 1994). Caffeine's direct effect on neuronal systems associated with arousal may explain its relatively selective effects on behaviors associated with alertness, such as vigilance and fatigue, and the possible absence of direct effects on other neural systems such as those regulating learning, memory and perception.

Optimal dose of caffeine during exposure to multiple stressors

Examination in aggregate of performance and mood data collected during this study (Fig. 2) suggests that the optimal dose of caffeine to improve cognitive function under such conditions is approximately 200 mg. It does not appear from the dose-response functions for caffeine that sufficient benefit is derived when a dose of 300 mg is employed, vs. a dose of 200 mg, for most of the tests administered. This suggestion is strongly supported by the statistical analyses that we conducted since on post hoc testing, when 300 mg was directly compared to 200 mg in the 1 h test session, they were never statistically distinguishable on any of the performance tests (Table 1). Vigilance and reaction time (Fig. 2a, b), as well as higher cognitive functions, as assessed by the matching-to-sample (with exception of time-out errors) and the repeated acquisition task, all seem to plateau as the dose of caffeine increases from 200 to 300 mg (Fig. 2c, d). Data from the marksmanship task also support the 200-mg dose recommendation (Fig. 2f). Non-significant benefits in performance in this test appear to be present and increase from the 100- to 200-mg dose, but at 300 mg the function begins to invert, and benefits are either less than with 200 mg or not present at all. It can be hypothesized that at doses higher than 300 mg adverse effects on marksmanship and mood would be observed, since these parameters were the least positively affected at 300 mg. Other cognitive functions have been found to degrade when doses of 400 or 500 mg caffeine are administered (Kaplan et al. 1997).

In contrast, it is clear there are significant benefits in using a 200-mg dose compared to a 100-mg dose. For example, there are only modest improvements in vigilance and reaction time (Fig. 2a, b) when the dose is increased from 200 to 300 mg, but these parameters improve substantially from 100 to 200 mg. Furthermore, in no instance was the 100-mg dose statistically different then placebo on post hoc testing.

The beneficial effects of caffeine on mood also appear to be maximal at 200 mg, with the exception of the fatigue subscale of the POMS, for which maximal benefit was seen at 300 mg (Fig. 2e). In a previous study of rested volunteers we found that caffeine's effects on mood often were maximal at intermediate doses (Amendola et al. (1998). Therefore over all behavioral parameters assessed in this study a dose of caffeine in the range of 200 mg appears to be optimal when performance is degraded by sleep loss and exposure to stressors. Among individuals who have developed tolerance to caffeine, a somewhat higher dose may be warranted since the SEAL trainees had low residual levels of caffeine (Fig. 1) at baseline and prior to Hell Week. Kaplan et al. (1997) administered 250 and 500 mg of caffeine to rested volunteers and found that cognitive performance and mood were optimal at the 250-mg dose.

Persistent effects of caffeine

One of the more surprising results of this study was the persistent effects of caffeine 8 h after administration. Visual vigilance, repeated acquisition, and POMS fatigue were all positively affected by caffeine during the final testing session. The saliva caffeine assays indicate levels resulting from the 300-mg dose after 8 h were intermediate between those produced by the 100- and 200-mg doses 1 h after administration (Fig. 1). This is consistent with the persistent behavioral effects at 8 h It has been suggested caffeine should be administered in sustained-release formulations when it is used to prevent performance degradation due to sleep loss (Patat et al. 2000). However, since it retains behavioral effects for 8 h when given in a standard formulation at a dose of 200 or 300 mg, a sustained release preparation may produce effects for much longer then desired. It should be noted, however, that the multiple stressors of Hell Week may have altered caffeine's pharmacokinetics or behavioral potency.

Conclusions

Caffeine had beneficial effects on a variety of behavioral parameters and mood states. Among volunteers exposed to severe sleep loss and other stressors moderate doses of caffeine improved both speed and accuracy components of visual vigilance performance and accuracy on a four-choice visual reaction time test. Performance on a task of working memory and learning, repeated acquisition, also improved. The use of caffeine did not disrupt marksmanship in spite of concerns it might decrease steadiness. No increase in self-reported adverse symptoms was present following caffeine administration. Unexpectedly, some of caffeine's effects on performance and mood persisted up to 8 h after administration.

Based on the findings of this study it is recommended that 200 mg caffeine be used to improve cognitive function that is degraded by sleep deprivation and exposure to severe environmental and operational stress. This dose improves key aspects of cognitive function, has a positive effect on mood and does not appear to pose any physiological or psychological risk. Other compounds that enhance cognitive performance during sleep deprivation and severe stress, such as amphetamine and modafinil, may be more potent than caffeine. However, their use requires greater medical supervision due to their controlled status, and they are more likely to produce undesirable side effects, especially amphetamine and closely related compounds (Akerstedt and Ficca 1997).

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