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The Effects of Caffeine and Aspirin on Mood and Performance

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Caffeine, in addition to being a food constituent, is also a common analgesic adjuvant that is used in combination with aspirin in certain over-the-counter preparations. Caffeine has previously been shown to significantly improve certain aspects of human performance, particularly sustained vigilance, when administered in low and moderate doses (32 to 256 mg). We therefore attempted to determine whether caffeine, in the dose (64 mg) found in some over-the-counter drugs, retains this beneficial property when combined with aspirin. We also measured self-reported mood state, using various standardized questionnaires, since caffeine has been reported to have both beneficial and adverse effects on alertness and anxiety. We observed that caffeine (64 mg), when added to aspirin (800 mg), significantly improves vigilance performance and increases self-reported efficiency when compared with either placebo or aspirin alone. As previously reported, this caffeine dose alone significantly increased vigilance and decreased reaction time. No adverse effects of caffeine were detected on any of the parameters that were assessed. This study therefore demonstrated that the addition of caffeine to aspirin, in a dose commonly employed in over-the-counter drugs, has significant beneficial consequences with respect to mood and performance.
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CONSIDERABLE controversy exists regarding the behavioral effects of the doses of caffeine found in over-the-counter drugs and foods. While it is clear that relatively high caffeine doses can exert both physiological and behavioral effects, there is little agreement regarding the xanthine's effects at the lower levels commonly found in foods and drugs. In some studies, doses of 75 to 500 mg improved performance and increased self-reported alertness.[1–3] However, other studies failed to detect behavioral effects of caffeine in this dosage range,[4–6] and such divergent findings have led to considerable confusion in reviews of the extensive literature on caffeine's actions.[7, 8] Some of the confusion may reflect the use of different subject populations and different behavioral tests, or of insufficient numbers of subjects. Uncontrolled confounding factors such as the extent of habitual caffeine use, the consumption of caffeine immediately preceding the experimental session, or the use of tobacco (since smoking substantially increases caffeine clearance rates)[9] may have also contributed to the numerous discrepancies in the literature.

In an effort to determine whether consistent behavioral effects of low and moderate oral caffeine doses (32, 64, 128, 256 mg) could be documented, we previously conducted a double-blind, placebo-controlled crossover study[10] on 20 healthy male volunteers using performance and mood tests that, based on results of previous studies, seemed most likely to be sensitive to the behavioral effects of caffeine at low doses.[1–3, 10] The subjects were healthy male volunteers aged 18 to 47. Habitual caffeine use was controlled by stratifying the subjects into low and moderate caffeine-consuming groups and excluding heavy users (defined as those individuals having a caffeine intake of more than 400 mg/day). Tobacco users were also excluded from the sample and, to control for caffeine use immediately preceding testing, the subjects were required to abstain from caffeine use for 12 hours prior to testing.

In that study it was found that caffeine at every dose administered, even the lowest dose (only 32 mg), significantly improved performance on a test of sustained vigilance (a modified version of the Wilkinson Auditory Vigilance Test) and a visual choice reaction time (RT) task (Four-choice Visual Reaction Time).

Having found that low and moderate doses of caffeine

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appear to consistently improve particular aspects of human performance, we conducted a study to determine whether caffeine, particularly in a dose of 64 mg, retained its beneficial effects when combined with 800 mg of aspirin. This combination is a currently available over-the-counter formulation. For exploratory purposes a higher dose of caffeine (128 mg) was also included in combination with aspirin.

Methods

This study was conducted using a double-blind, placebo-controlled design. Twenty male subjects, aged 18 to 35, in good health were tested after they gave written informed consent. Prior to admission to the study, all subjects completed written questionnaires to evaluate their usual patterns of consumption of coffee, soft drinks, and caffeine-containing medication. Based on their responses, they were divided into three groups: those who generally consumed 100 mg or less of caffeine per day, those who consumed 100 to 400 mg/day, and those consuming over 400 mg/day. Only individuals from the first two groups were admitted to the study; tobacco users were also excluded.

All subjects admitted to the study were tested on a battery of mood and performance tests on six different occasions. Each session was separated from the previous one by at least 2 days. The first session served as a practice session. On the subsequent five sessions each subject received in a counterbalanced order determined by a Latin-square design: (1) caffeine (64 mg); (2) aspirin (800 mg); (3) caffeine (64 mg) and aspirin (800 mg); (4) caffeine (128 mg) and aspirin (800 mg); and (5) placebo.

Subjects fasted from 8:00 p.m. the evening before testing and ingested the experimental agent at 8:00 a.m. the next morning under the supervision of a nurse. Testing began at 9:00 a.m. and lasted 2 hours. Subjects were instructed to abstain from caffeine consumption for 24 hours prior to each test session.

The performance variables measured included reaction time (both auditory and visual), motor performance, and vigilance. Self-report mood questionnaires were also administered. The choice of specific mood and performance tests were based on previous studies that have examined the behavioral effects of moderate doses of caffeine, especially our own recent dose-response study.[10]

Behavioral Tests Administered

Performance tests

Four-choice Visual Reaction Time. This test resembles the Wilkinson four-choice RT task and is a measure of visual vigilance.[11] Subjects are presented with a series of visual stimuli at one of four different spatial locations on a cathode-ray tube (CRT) screen. The subject must correctly indicate, by striking one of four adjacent keys on a microcomputer keyboard, the correct location of each stimulus. Five hundred trials are administered. In addition to response latency for each trial, errors of omission (response latency greater than 1 second) and commission are recorded. The test requires about 10 minutes to complete.

Wilkinson Auditory Vigilance Test. This test is a measure of sustained auditory vigilance.[12] Every 2 seconds, for a 1-hour time period, a tone which is 400 msec in duration is presented via headphones. To mask out extraneous noise a background of white noise is also presented through the headphones. Forty of these tones are approximately 70 msec shorter than the rest. The subject's task is to correctly identify these 40 "signal" tones by pressing a key on the computer keyboard when he believes a signal tone has been presented. In addition to the number correct, false alarms (pressing the key when a "signal" stimulus has not been presented) are also recorded. Unlike the original version of this test, the difficulty is adjusted for each subject by varying the duration of the test stimuli. During the practice session, each subject's performance is adjusted to a criterion of approximately 50% correct. This is accomplished by varying the duration of the test stimuli: slightly decreasing their duration decreases the difficulty of the task by reducing their similarity to the other tones. Once a test stimulus duration was selected for a subject, it was not changed for the rest of the study. Therefore, this test is adaptive to the extent that each subject initially performs at about the same level.

Tapping Test. For this motor task the subject must alternately tap, with a hand-held metal stylus, two wedge-shaped targets separated by 1 cm. The subject was required to perform this task as rapidly as possible for 2 minutes.

Simply Auditory Reaction Time. In this microcomputer-administered test, the subject responded as rapidly as possible to the onset of a 75 dB (SPL), 1900 Hz tone.[13] After five warmup trials, 125 test trials were presented in rapid succession. A visual cue, presented on a CRT, indicated the start of a trial. Both commission errors (responding prior to the termination of the stimulus tone) and errors of omission (response latency greater than one sec) were recorded.

Mood scales

Profile of Mood States (POMS). The POMS is a self-report mood questionnaire that, when analyzed, yields six factors: tension-anxiety, depression-dejection, anger-

hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment.[14] The test consists of 65 adjectives each of which is rated on a five-point scale. The POMS has been employed in many psychopharmacological studies and is sensitive to the effects of many different classes of psychoactive drugs, including hypnotics and stimulants.

Visual Analogue Mood Scales (VAMS). The VAMS is a self-report mood questionnaire that measures the extent to which a subject experienced each of three mood states: alert, sad, and calm.[13, 15] Each of 32 adjectives was rated by the subject by moving a pointer along a horizontal line presented on a CRT. The minimum extent of a particular mood was indicated by placing the pointer on the extreme left of the line, and the maximum by placing it on the right.

Nestle Visual Analog Mood Scale. This seven-item, paper and pencil bipolar scale has previously been shown to be sensitive to the effects of caffeine.[3]

Stanford Sleepiness Scale (SSS). This self-rated seven-point scale was designed to quantify the progressive stages of the alertness-sleepiness continuum.[16] It has been used in a number of psychopharmacological studies and is sensitive to the effects of hypnotics.

Results

The means (±SEM) for all the mood and performance tests administered are presented in Tables 1 and 2. The data from these tests were analyzed using complex Latin-square analyses of variance. There were significant differences attributable to drug treatment on three of the performance tests administered: modified Wilkinson Auditory Vigilance ($p < 0.01$), simple auditory RT ($p < 0.0005$), and tapping with the preferred hand ($p < 0.05$) (Table 3). Significant treatment effects were also detected by the vigor subscale of the POMS ($p < 0.025$), the Stanford Sleepiness scale ($p < 0.05$), the alertness subscale of the VAMS ($p < 0.05$) as well as various individual items from the Nestle analog scales (Table 3). Additional tests to compare specific treatments were then conducted. The comparisons of interest were (1) caffeine (64 mg) and aspirin versus aspirin, (2) caffeine (64) and aspirin versus placebo, and (3) caffeine (64 mg) versus placebo. Two-tailed, multiple comparison *t*-tests were employed for these comparisons and a number of these contrasts were statistically significant (Table 4).

Performance on the Wilkinson Auditory Vigilance task was significantly improved by the caffeine (64 mg) and aspirin (800 mg) combination compared to placebo and also compared to aspirin alone ($p < 0.05$). Caffeine (64 mg) alone also significantly improved performance on this task ($p < 0.01$). We have previously shown that this test is very sensitive to the positive effects of caffeine at this dose and also at higher and lower doses (32, 64, 128, and 256 mg).[10] Performance also improved on another task, simple auditory reaction time, when the aspirin (800 mg) and caffeine (64 mg) combination was compared to placebo ($p < 0.02$) and when caffeine alone was compared to placebo ($p < 0.05$) (Table 4). We had not previously observed a statistically significant effect of caffeine on this test, but other investigators have.[1]

Certain self-reported mood states also significantly improved when caffeine alone was administered or caffeine and aspirin were given in combination (Table 4). On the Nestle bipolar visual analog scale, previously shown to be sensitive to caffeine at a dose of 100 mg,[3] significant effects of the treatments of interest were noted. On the "muddled/clearheaded" scale, the caffeine (64 mg) and aspirin (800 mg) combination signifi-

TABLE 1. Means ± SEM and time after drug administration performance tests

Test name	Aspirin (800 mg) + caffeine (64 mg)	Aspirin (800 mg) + caffeine (128 mg)	Caffeine (64 mg) alone	Aspirin (800 mg) alone	Placebo	Time (min)
Four-choice RT (500 trials) (1st)	402.15	390.66	395.82	390.19	398.80	50
	±11.90	±9.00	±11.20	±13.60	±13.50	
Simple auditory RT (msec) (1st)	135.54	134.38	139.99	136.10	139.46	60
	±5.70	±5.20	±5.30	±5.00	±6.20	
Wilkinson auditory vigilance:						
total hits	21.45	20.75	22.65	18.8	18.7	65
	±1.45	±1.71	±1.77	±1.75	±1.66	
Simple auditory RT (msec) (2nd)	133.88	126.59	134.29	132.28	140.94	135
	±4.90	±5.23	±4.75	±4.43	±6.98	
Four-choice RT (500 trials) (2nd)	396.03	386.65	395.68	393.13	397.59	147
	±12.20	±9.90	±9.80	±10.90	±11.30	
Tapping 2 min	599.90	609.80	602.00	586.90	598.20	157
Preferred	±11.10	±9.40	±11.40	±10.20	±10.30	
Nonpreferred	520.60	533.30	523.05	518.70	516.55	
	±9.81	±11.11	±11.79	±12.35	±11.77	

TABLE 2. Means ± SEM and time after drug administration for mood questionnaires

Test name	Aspirin (800 mg) + caffeine (64 mg)	Aspirin (800 mg) + caffeine (128 mg)	Caffeine (64 mg) alone	Aspirin (800 mg) alone	Placebo	Time (min)
VAMS						
Alert	37.37 ±1.84	40.89 ±2.01	39.02 ±1.65	35.36 ±1.94	36.22 ±1.67	60
Sad	14.80 ±1.51	11.96 ±1.88	15.60 ±1.60	15.73 ±1.84	14.66	
Calm	20.94 ±1.59	22.05 ±1.66	19.89 ±1.62	21.25 ±1.91	21.27 ±1.66	
POMS scales						
Vigor	14.20 ±1.67	15.80 ±1.51	14.45 ±1.60	11.55 ±1.26	11.60 ±1.20	130
Tension	7.40 ±1.13	6.00 ±1.07	5.90 ±1.03	6.20 ±0.97	6.45 ±1.06	
Depression	4.70 ±1.40	3.10 ±1.04	4.60 ±1.69	4.40 ±1.14	3.85 ±1.00	
Anger	3.15 ±1.20	3.35 ±1.46	5.45 ±2.10	3.00 ±0.74	2.75 ±0.84	
Fatigue	9.40 ±1.76	6.55 ±1.37	8.55 ±1.50	11.25 ±1.87	9.90 ±1.60	
Confusion	5.80 ±0.96	4.45 ±0.89	5.60 ±0.92	6.65 ±0.76	6.70 ±0.88	
SSS	3.00 ±0.36	2.50 ±0.29	2.85 ±0.30	3.60 ±0.29	3.55 ±0.28	133
Nestle Analog Scales						
Muddled/clearheaded	8.61 ±0.62	8.91 ±0.72	8.31 ±0.71	6.92 ±0.54	7.07 ±0.63	145
Inefficient/efficient	8.25 ±0.76	9.20 ±0.62	8.50 ±0.62	7.33 ±0.60	7.01 ±0.57	
Tired/energetic	6.20 ±0.78	7.60 ±0.86	7.24 ±0.79	5.025 ±0.63	5.28 0.74	
Lethargic/vigorous	6.84 ±0.85	8.76 ±0.71	7.77 ±0.69	5.66 ±0.54	5.78 ±0.64	
Unimaginative/imaginative	7.88 ±0.64	9.03 ±0.55	7.82 ±0.54	7.11 ±0.54	7.27 ±0.61	
Listless/full of go	6.87 ±0.71	8.68 ±0.59	7.44 ±0.68	5.92 ±0.58	6.26 ±0.66	
Ill at ease/fine	9.01 ±0.67	9.98 ±0.58	9.16 ±0.70	8.38 ±0.58	8.05 ±0.69	

TABLE 3. Significant drug effects on analysis of variance

Dependent variable	*p* value
Performance tests	
Wilkinson vigilance	<0.01
Auditory RT (2nd)	<0.0005
Tapping—preferred hand	<0.05
Mood questionnaires	
POMS—vigor	<0.025
SS Scale	<0.05
VAMS—alert	<0.05
Nestle analog scales	
Lethargic/vigorous	<0.0025
Muddled/clearheaded	<0.01
Tired/energetic	<0.025
Unimaginative/imaginative	<0.05
Listless/full of go	<0.005
Inefficient/efficient	<0.01

cantly increased self-reported clearheadedness ($p < 0.05$) compared to placebo and also aspirin (800 mg) alone. The "inefficient/efficient" bipolar scale also detected a significant improvement when aspirin and caffeine (64 mg) were compared to placebo ($p < 0.05$). Two other analog scales detected positive effects of caffeine (64 mg) versus placebo: "tired-energetic" ($p < 0.05$) and "lethargic/vigorous" ($p < 0.01$). The vigor subscale of the POMS and the SSS also detected significant positive effects of caffeine (64 mg) versus placebo ($p < 0.05$) (Table 4). No adverse effects of caffeine, e.g., an increase in anxiety, were noted on any of the mood questionnaires that included such scales (the POMS tension/anxiety scale and the VAMS calmness scale) as previously observed.[10]

Discussion

It can be concluded that when caffeine is administered in a dose of 64 mg, it significantly improves cer-

TABLE 4. Post-hoc comparisons with associated significance level

Tests	Caffeine (64 mg) + aspirin vs. aspirin	Caffeine (64 mg) + aspirin vs. placebo	Caffeine (64 mg) vs. placebo
Performance			
Wilkinson vigilance	0.05	0.05	0.01
Auditory RT	NS[a]	0.02	0.05
Mood			
POMS—vigor	NS	NS	0.05
SSS	NS	NS	0.05
Nestle analog scales			
Lethargic/vigorous	NS	NS	0.01
Muddled/clearheaded	0.05	0.05	NS
Tired/energetic	NS	NS	0.05
Inefficient/efficient	NS	0.05	0.02

[a]NS = not significant.

tain aspects of human performance and also appears to positively alter self-reported mood state. Additionally, when this dose of caffeine (64 mg) is combined with aspirin, its beneficial effects on performance and mood are still present, compared to either aspirin alone or placebo. The effects of caffeine, and caffeine in combination with aspirin, appeared to be consistent with regard to the particular aspects of performance and mood altered. The performance of our subjects improved on tests of vigilance and RT. Concurrently, subjects reported they felt more clearheaded (Nestle analog scale), less inefficient (Nestle analog scale), and for some comparisons, more vigorous (POMS) and less sleepy (SSS). Many mood scales were not significantly affected by our treatments. The absence of effects on these parameters is probably not dose-related since in our previous study, which included higher doses of caffeine, such mood effects were also not detected.

The results of this study are in agreement with the results of the prior dose-response study we conducted with caffeine.[10] In that study all doses of caffeine (32, 64, 128, and 256 mg) improved performance on two vigilance tests (Wilkinson Auditory Vigilance test and four-choice Visual Reaction Time Task). The Wilkinson Auditory Vigilance test was especially sensitive to caffeine. This test again proved to be sensitive to the effects of caffeine compared to placebo. The key comparisons of interest in this study were caffeine (64 mg) and aspirin (800 mg) versus placebo and also caffeine and aspirin versus aspirin alone. Our version of the Wilkinson Auditory Vigilance test detected significantly improved performance when caffeine was combined with aspirin compared to placebo and aspirin alone. Also, caffeine alone (64 mg) was again found to improved performance as we have previously reported.[10] This demonstrates that caffeine (64 mg) alone or in combination with aspirin has significant beneficial effects on the ability of healthy individuals to perform specific behavioral tasks. Numerous "real-life" tasks require sustained vigilance, including driving motor vehicles and operating various types of industrial equipment. Caffeine (200 mg) has, in fact, been shown to improve performance in a highly realistic, simulated automobile driving paradigm.[17] The performance of many tasks that require attention to irregularly occurring signals might be improved by caffeine administration at doses well below 200 mg. It should also be noted that caffeine in doses of 125 to 500 mg has been found to antagonize some of the sedative properties of at least one of the benzodiazepines[2] and could perhaps, under certain circumstances, be a useful adjuvant to various drugs with sedative properties.

Unlike our initial study,[10] this study detected significant positive effects of caffeine on mood state as well as performance. For example, subjects felt significantly more "efficient" and "clearheaded" on these items of the Nestle analog scales, as well as more vigorous (POMS vigor scale) and less sleepy (SSS), after various treatments that included 64 mg of caffeine compared with placebo. These effects were consistent with the changes in performance that were observed in this study. Similar changes in mood have been previously documented but only at somewhat higher doses of caffeine than we administered.[1, 3, 4]

It can be concluded that 64 mg of caffeine, alone or in combination with aspirin, significantly improves human performance and mood. These beneficial effects are likely to be amplified in a patient population suffering from the "malaise" (suboptimal mood and performance) associated with many of the common clinical conditions aspirin is used to treat.

We believe we have now established a standardized methodology for demonstrating beneficial effects of low and moderate doses of caffeine. Our methods are likely to be applicable to a wide range of situations and a variety of products that contain caffeine.

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