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Effects of caffeine on alertness

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Abstract. The alerting effects of caffeine were assessed using a standard physiological measure of daytime sleepiness/alertness, the Multiple Sleep Latency Test (MSLT). Healthy young men ($n=24$) were randomly assigned to receive caffeine 250 mg or placebo administered double blind, at 0900 and 1300 hours on each of 2 days. On the 3rd day both groups received placebo to test for conditioning to the alerting effects of caffeine. Each day sleep latency was measured at 1000, 1200, 1400, and 1600 hours and performance (divided attention at 1030 hours and auditory vigilance at 1430 hours) was assessed. Caffeine increased sleep latency (i.e., improved alertness) and auditory vigilance performance compared to placebo. Tolerance to the effects of caffeine on sleep latency developed over the four administrations. On the conditioning test (day 3) the group receiving caffeine the previous two days was more alert and performed better than the placebo group.

Key words: Multiple sleep latency test – Caffeine – Alertness – Tolerance – Conditioning

To date there have been no controlled studies which directly measure the effects of caffeine on daytime alertness. The Multiple Sleep Latency Test (MSLT) has been employed successfully in a variety of experimental and clinical situations to provide a direct, objective determination of daytime sleepiness/alertness (Carskadon and Dement 1982). The MSLT measures the latency to polygraphically defined sleep in 20 min opportunities given at 2 h intervals across the day. The MSLT is a reliable measure which is sensitive to the alerting effect of sleep extension and the alerting effects of naps of varying duration after sleep deprivation (Lumley et al. 1986). CNS stimulant drugs improve the excessive daytime sleepiness of sleep disorders patients as measured by the MSLT (Mitler et al. 1986). The only study to date which has assessed the effects of caffeine using the MSLT compared caffeine to ethanol but used no placebo condition (Lumley et al. 1987).

While most of the caffeine literature indicates that caffeine has alerting effects (Karacan et al. 1976; Nicholson and Stone 1980) there are studies failing to show effects, particularly at the lower doses (Clubley et al. 1979). Some of the confusion may reflect uncontrolled confounding factors such as the extent of habitual caffeine use in the population being studied. This raises the question as to what extent tolerance develops to the alerting effects of caffeine. Few objective laboratory studies have assessed human tolerance to the effects of caffeine with repeated administration. Tolerance development to the effects of caffeine might be expected, but the question is whether that occurs rapidly over a small number of administrations.

Another important aspect of the effects of caffeine is the extent to which conditioning to the alerting effect of caffeine may take place. Administration of drugs necessarily occurs in the context of a variety of concurrent stimulus cues (i.e., the caffeine vehicle, the coffee beverage), which can become associated with the primary effects of the drug itself in a Pavlovian conditioning model. In fact, Pavlov himself proposed that a drug can serve as an unconditioned stimulus (Pavlov 1925). Only a few studies have assessed conditioning of stimulant drugs. The conditioned effects of cocaine and amphetamines have been tested using the classical conditioning paradigm and the results have demonstrated that conditioning to these drugs occurs (Hinson and Poulos 1981; Barr et al. 1983; Chait et al. 1985, 1986). There are no data on conditioned responses to caffeine in humans.

This study was designed to assess the alerting effects of caffeine (250 mg) relative to placebo, using the standard physiological measure of daytime sleepiness/alertness, the MSLT and psychomotor performance measures. Additionally, the study was designed to analyze caffeine tolerance over a few repeated administrations. Finally, the study design also incorporated an assessment of the possibility of conditioned responses to caffeine.

Methods

Subjects. The subjects were 24 normal sleeping, non-smoking men, aged 21–36 years recruited from nearby colleges. All were in good health based on a brief history and physical examination and had normal blood and urine laboratory test results (which included a screening for drug use). They reported no tobacco use, a maximum caffeine intake of 250 mg a day, nocturnal sleep times of 6–8 h, sleep latencies of less than 30 min, generally consistent bedtimes and risetimes (not varying night-to-night by >2 h), and an avoidance of habitual napping. All subjects had normal sleep on one 8 h night of polysomnography (including nasal/oral to monitor breathing pattern and leg electrodes to monitor for periodic leg movements). A MSLT was performed the following day (screening criteria described below). All subjects signed an informed voluntary consent and were paid for participation.

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Table 1. Treatment schedule and daily assessment schedule

Treatments

	Day 1		Day 2		Day 3	
Group	Caff	Plac	Caff	Plac	Caff	Plac
0900 hours	250 mg	Plac	250 mg	Plac	Plac	Plac
1300 hours	250 mg	Plac	250 mg	Plac	Plac	Plac

Daily schedule

0730	Risetime
0800	Breakfast
0900	Tx administration
1000	Latency test
1030	Divided attention
1200	Latency test
1230	Lunch
1300	Tx administration
1400	Latency test
1430	Auditory vigilance
1600	Latency test

Design. This is a mixed design experiment (see Table 1). Subjects were assigned randomly to placebo or caffeine treatments administered double blind. Each subject received the appropriate treatment on 2 consecutive days. The caffeine group experienced four pairings of caffeine effects with concurrent stimulus cues over the 2 days. On the 3rd day, subjects in both groups received placebo. This 3rd day treatment allowed for an assessment of possible conditioning to the effects of caffeine.

Procedure. For the screening subjects reported to the laboratory one evening at 2230 hours. They spent 8 h in bed while being polygraphically monitored using standard procedures (Rechtschaffen and Kales 1988). Subjects were excluded if they exhibited any evidence of sleep disorders. The following day, they were tested for level of daytime sleepiness at 1000, 1200, 1400, and 1600 hours using the standard MSLT procedures (Carskadon et al. 1986). For these and all subsequent latency tests, the subjects were placed in beds in quiet, darkened rooms and instructed to close their eyes, relax, and try to fall asleep. Subjects were awakened after 1 min of unambiguous stage 1 sleep, the first sign of stage 2 or REM sleep, or 20 min continuous wake, according to the standards of Rechtschaffen and Kales (1968). Subjects were admitted into the study if they showed an average sleep latency on the screening MSLT of <10 min. Moderately sleepy subjects were chosen for this study to begin to explore the limits of the alerting effects of caffeine and to potentially avoid the 20 min measurement ceiling for the MSLT. The screening average daily sleep latency of the placebo group was 5.55 ± 2.53 min and for the caffeine group it was 5.61 ± 2.33 min.

In addition to the MSLT two psychomotor tests were also used to evaluate the alerting effects of caffeine. At 1030 hours, a 15 min divided attention task was administered on an Apple II computer. For this task subjects must track a moving target across the video screen using a joy stick and simultaneously press a button in response to the appearance of a white circle on the periphery of the screen or at the center of the moving target. At 1430 hours the subjects performed a 40-min auditory vigilance task. For this task the subject must detect long tones occurring randomly within a continuous series of short tones. At screening each group received two practice sessions on the performance tests and there were no differences between the caffeine and placebo group in divided attention and vigilance performance and no days effects in the placebo group suggestive of learning beyond the practice session.

Those subjects passing the screening were then scheduled for 3 consecutive study days. The daily assessment schedule is outlined in Table 1. Every study day, subjects went to bed at 2330 hours and arose at 0730 hours. This ensured an 8 h time in bed and a constant time from sleep offset until the first latency test. During each of the 3 nights of the study, the subjects slept in the laboratory, and each wore a movement-activated recording device attached to the dominant wrist. The use of the wrist actigraph allows for a determination of minutes of activity or inactivity during bedtime. The actigraph has been shown to predict polysomnographically determined sleep or wake with 93% accuracy in healthy normal sleepers (Levine et al. 1986).

Upon awakening subjects ate breakfast, which included a roll and orange juice. At 0900 hours subjects received either caffeine or placebo. The caffeine treatment consisted of 250 mg caffeine powder dissolved in 300 ml hot water and 97% caffeine-free instant coffee (Taster's Choice). The placebo group received the 97% caffeine-free instant coffee with 300 ml hot water. Subjects were allowed to sweeten the beverage with saccharin and use a non-dairy creamer if they desired. Subjects were instructed to pace their consumption of the beverage over a 15-min period. The assessment as outlined in Table 1 was conducted on each of the 3 study days.

Throughout the study subjects were instructed to avoid all outside caffeine containing foods and beverages. They were also asked to maintain their regular exercise regimen during the study and to avoid all drug use (prescription, illicit, and over-the-counter) 1 week prior to and during the study. Subjects avoided eating more than the required breakfast until after the 1200 hour latency test. They were monitored to ensure wakefulness between tests, and were told to avoid napping during the evening at home.

Sleep latency was scored as minutes to the first 30 s epoch of sleep, according to the Rechtschaffen and Kales (1968) criteria, by raters unaware of the treatments or the day of the study. Data were analyzed using mixed design multivariate analyses of variance (SAS Institute), with the between group variable being the caffeine or placebo treatment, the within group variable the days of testing and the dependent variables being the mean MSLT latency and the various performance measures. The probabilities reported for the repeated measures effects are corrected by the Greenhouse-Geisser method. Post hoc comparisons were done using the Duncan procedures.

Results

The effects of caffeine on average daily sleep latency and on sleep latency for each separate latency test are illustrated in Fig. 1. A mixed design MANOVA was conducted to compare average daily sleep latency for day 1 and 2 between the two groups. Average daily sleep latency was significantly greater in the caffeine compared to the placebo group

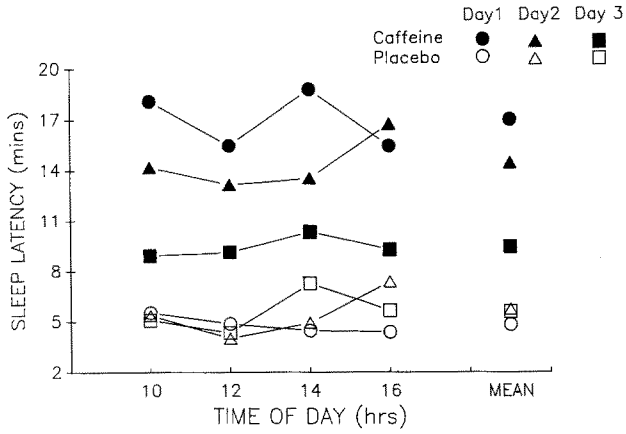

Fig. 1. The effects of caffeine and placebo on sleep latency for each latency test and the mean of the four tests on day 1, 2, and 3

Table 2. Auditory vigilance performance

	Day 1		Day 2		Day 3	
Group	Caff	Plac	Caff	Plac	Caff	Plac
Mean RT	396 (152)	583 (287)	415 (163)	567 (266)	428 (245)	631 (313)
# Errors	1.5 (2.8)	1.8 (2.4)	1.0 (1.5)	2.8 (2.7)	1.2 (1.7)	4.3 (5.4)
Z-Scores	+0.17 (0.68)	−0.05 (0.63)	+0.25 (0.31)	−0.19 (0.52)	+0.17 (0.46)	−0.39 (0.85)

Data are means (±SD)
Mean RT = reaction time over the 40 min task (ms); Z-Scores = mean RT and # of errors combined

($F=78.06$; $df=1,22$; $P<0.0001$). There was no main effect of days but the analysis revealed a significant days by group interaction ($F=6.85$; $df=1,22$; $P<0.016$) which will be discussed later.

Vigilance performance measures also demonstrated significant effects of caffeine. The effects of caffeine on reaction time and accuracy as measured with the vigilance test are presented in Table 2. A mixed design MANOVA was conducted comparing overall vigilance performance over days between groups. Reaction time and number of errors data were converted independently to z-scores and the two z-scores were averaged to a single overall score. The z-score data were significantly improved in the caffeine group compared to the placebo group ($F=4.49$; $df=1,22$; $P<0.05$). There was no days effect or a days by group interaction. Divided attention measures showed no significant effects.

While the present study was not designed to specifically assess the time course of the effects of caffeine, some indication as to the duration of the increased alertness can be obtained from this study. To address the question of the time course of the effect of caffeine on daytime sleep latency, a mean of the two latency tests on days 1 and 2 which were conducted 1 h after caffeine administration versus the mean of the two latency tests (day 1 and 2) conducted 3 h post-caffeine administration was compared. A mean of the two latency tests was used since single latency tests have been found to have reduced reliability (Zwyghuizen-Doorenbos et al. 1988). A mixed design MANOVA was conducted to compare caffeine effects 1 and 3 h post-caffeine or placebo administration. The analysis yielded a significant caffeine effect as discussed above. But pertinent to the time course question a significant interaction was found also ($F=6.89$; $df=1,22$; $P<0.02$). Latency declined from 18.4 min 1 h post-administration to 15.4 min 3 h post-administration in the caffeine group. The placebo group showed no change in latency from 1 h to 3 h post-administration. It is important to note that 3 h latencies of the caffeine group remained higher than that of the placebo group ($P<0.05$), indicating that caffeine effects, although considerably diminished from 1 h post-administration, remained at 3 h post-administration.

With regard to immediate tolerance, which is the second major question of this study, there was no main effect of days in the omnibus MANOVA, but the analysis revealed a significant days by group interaction ($F=6.85$; $df=1,22$; $P<0.02$). Post hoc comparisons showed a small decline in latency within the caffeine group from day 1 to day 2 ($P<0.04$). The placebo group did not change from day 1 to day 2. To examine the question of tolerance more closely the immediate (1 h post-administration) alerting effects of caffeine after each of the four administrations was examined. As expected a group effect was found ($F=71.55$; $df=1,22$; $P<0.0001$), but critical to the question of tolerance is the interaction of group by administration which was significant ($F=2.93$; $df=1,22$; $P<0.04$). The sleep latency of the caffeine group declined over the four administrations, while the placebo group showed no differences over those administrations (see Fig. 1). A polynomial regression analysis was used to characterize the change in the effects of caffeine over the four administrations. There was a significant linear component ($F=4.81$; $df=1,22$; $P<0.05$), but no quadratic or cubic components in the sleep latency decline with administration. Latency after the fourth administration in the caffeine group was still significantly higher than that of the placebo group.

The possible conditioned effects of caffeine were assessed with a mixed design MANOVA analyzing mean sleep latency on days 1 and 3. These effects are illustrated in Fig. 1. There was a significant group effect ($F=53.08$; $df=1,22$; $P<0.0001$), days effect ($F=18.77$; $df=1,22$; $P<0.0001$), and a days by group interaction ($F=26.23$; $df=1,22$; $P<0.0001$). Post hoc comparisons revealed that on day 3 the caffeine group continued to have significantly higher latencies ($P<0.004$) than the placebo group. Within the placebo group there were no differences among days. A similar analysis of vigilance performance (z-scores) showed a more profound conditioning effect as indicated by a significant group effect ($F=4.49$; $df=1,22$; $P<0.05$) and the absence of a significant days effect or interaction. Even on day 3 (placebo administration) the caffeine group performed as well as on day 1 and better than the placebo group (see Table 2).

Discussion

The major finding of this study is that caffeine increases daytime alertness, as measured by the MSLT, in moderately sleepy, normal subjects. It also increased auditory vigilance performance which is a replication of previous research (Clubley et al. 1979; Liebermann et al. 1987). The results showed an increased average daily sleep latency as well as increased latency on each of the four latency tests. On the vigilance task mean reaction time was decreased, and subjects missed fewer tones with caffeine relative to placebo.

This is the first time that an objective and direct measure of daytime sleepiness/alertness has been used to demonstrate the alerting effects of caffeine relative to placebo.

Moderately sleepy subjects were used in this study to avoid a possible ceiling effect of caffeine on the MSLT. Each latency test of a MSLT is limited to 20 min and consequently caffeine effects could become skewed by this MSLT ceiling. The use of moderately sleepy subjects allowed for scores after caffeine administration to fall entirely within the range of the MSLT. However, the question then may arise as to how unusual this sample of subjects may be. These subjects were normal sleepers based on our screening and while sleepy, they fall within the lower half of the distribution of MSLT scores in healthy young males (Levine et al. 1988). Consequently, these subjects do not represent an extremely unusual sample.

A previous objective study of the daytime effects of caffeine on human blood pressure and urinary catecholamine levels demonstrated nearly complete tolerance within 3 days of administering 250 mg caffeine thrice daily, with meals (Robertson et al. 1981). In the present study the linear decrease in post administration MSLT scores for the caffeine (250 mg each of four administrations) group already demonstrated a developing tolerance to the alerting effects of caffeine within the four caffeine administrations. Thus tolerance to the effects of caffeine is demonstrated by using the MSLT, a direct objective measure of sleepiness/alertness and that tolerance occurs rapidly.

A provocative finding of this study is that the caffeine group was significantly more alert than the placebo group upon receiving placebo on the 3rd day. One possible interpretation for these results is that the contextual stimuli (possibly the 97% caffeine-free vehicle, Taster's Choice coffee beverage) that accompanies the caffeine administration became capable of eliciting a conditioned alerting response. These data are the first step in demonstrating a conditioned alerting effect of caffeine. To reach the final conclusion that caffeine conditioning occurs, a further demonstration of the extinction of the conditioned effects will be necessary. Performance and alertness in the caffeine group with repeated exposure to the 97% caffeine-free vehicle in the absence of caffeine would be expected to return to the placebo group level and the screening level of the caffeine group. At screening the two groups did not differ on any of the parameters.

An alternative hypothesis is that residual caffeine or its metabolites may have accumulated over the 2 days of administration. However, this explanation is not likely in the light of the known pharmacokinetics (half-life = 5.4 + 2.5 h) of caffeine and metabolites, at the dose (500 mg per day) used in this study (Tang-Liu et al. 1982). It also could be suggested that the administration of caffeine in some way altered the circadian rhythm of sleepiness/alertness. Because latency testing did not continue past 1600 hours, this hypothesis can not be ruled out.

In summary, caffeine clearly improves both alertness and vigilance performance as objectively measured. On days 1 and 2, subjects given caffeine were measurably more alert than those given placebos as demonstrated by the MSLT. Additionally alerting effects of caffeine were demonstrated by increased accuracy and decreased reaction times on vigilance performance measures. Tolerance to the daytime alerting effects of caffeine was demonstrated by the linear decreasing trend in post-administration MSLT scores. The data also suggested conditioned alerting responses to caffeine developed. Further investigation is planned to confirm the presence of conditioning to the effects of caffeine.

References

Barr GA, Sharpless NS, Cooper S, Schiff SR, Paredes W, Bridger WH (1983) Classical conditioning, decay and extinction of cocaine-induced hyperactivity and stereotype. Life Sci 33:1341–1351

Carskadon MA, Dement WC (1982) The multiple sleep latency test: what does it measure? Sleep 5:S67–S72

Carskadon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S (1986) Guidelines for the Multiple Sleep Latency Test (MSLT). A standard measure of sleepiness. Sleep 9:518–524

Chait LD, Uhlenhuth EH, Johanson CE (1985) The discriminative stimulus and subjective effects of *d*-amphetamine in humans. Psychopharmacology 86:307–312

Chait LD, Uhlenhuth EH, Johanson CE (1986) The discriminative stimulus and subjective effects of *d*-amphetamine, phenmetrazine and fenfluramine in humans. Psychopharmacology 89:301–306

Clubley W, Bye CE, Henson TA, Peck AW, Riddington CJ (1979) Effects of caffeine and cyuclizine alone and in combination on human performance, subjective effects and EEG activity. Br J Clin Pharmacol 7:157–163

Hinson RE, Poulos CX (1981) Sensitization to the behavioral effects of cocaine: modification by Pavlovian conditioning. Biochem Behav 15:559–562

Karacan I, Thornby JI, Anch M, Booth GH, Williams RL, Salis P (1976) Dose-related sleep disturbances induced by coffee and caffeine. Clin Pharmacol Ther 20:682–689

Levine B, Moyles T, Roehrs T, Fortier J, Roth T (1986) Actigraphic monitoring and polygraphic recording in determination of sleep and wake. Sleep Res 15:247

Levine B, Roehrs T, Zorick F, Roth T (1988) Daytime sleepiness in young adults. Sleep 11:39–46

Lieberman HR, Wurtman RJ, Emde GG, Roberts C, Coviella ILG (1987) The effects of low doses of caffeine on human performance and mood. Psychopharmacology 92:308–312

Lumley M, Roehrs T, Zorick F, Lamphere J, Roth T (1986) The alerting effects of naps in sleep-deprived subjects. Psychophysiology 23:403–408

Lumley M, Roehrs T, Asker D, Zorick F, Roth T (1987) Ethanol and caffeine effects on daytime sleepiness/alertness. Sleep 10:306–312

Mitler MM, Shafor R, Hajdukovich R, Timms RM, Browman CP (1986) Treatment of narcolepsy: objective studies on methylphenidate, pemoline, and protriptyline. Sleep 9:260–264

Nicholson AN, Stone BM (1980) Heterocyclic amphetamine derivatives and caffeine on sleep in man. Br J Clin Pharmacol 9:195–203

Pavlov IP (1927) Conditioned reflexes. Oxford University Press, London

Rechtschaffen A, Kales A (1968) A manual of standardized terminology techniques and scoring system for sleep stages of human subjects. National Institutes of Health Publications 204, Government Printing Office, Washington DC

Robertson D, Wade D, Workman R, Woosley RL, Oates JA (1981) Tolerance to the humoral and hemodynamic effects of caffeine in man. Clin Invest 67:1111–1117

Tang-Liu DD, Williams RL, Riegelman S (1983) Disposition of caffeine and its metabolites in man. J Pharmacol Exp Ther 224:180–185

Zwyghuizen-Doorenbos A, Roehrs T, Schaefer M, Roth T (1988) Test-retest reliability of the MSLT. Sleep 11:562–565

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