

## Caffeine Use as a Model of Acute and Chronic Insomnia

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**Summary:** It was hypothesized that the metabolic effects of caffeine, which can be objectively measured (i.e. physiological, "arousal"), could be used to develop a physiological arousal model of chronic insomnia in a group of normal young adults. Twelve normal young adult males participated for 11 nights after laboratory adaptation. Subjects received 400 mg of caffeine three times a day for 7 nights and days. As predicted, the use of caffeine resulted in increased metabolic rate. Sleep efficiency was significantly reduced by caffeine and multiple sleep latency tests (MSLTs) were significantly increased. Some adaptation to the metabolic, sleep efficiency, and MSLT effects of caffeine was seen over the week of administration. Withdrawal effects (i.e. rebound sleep or sleepiness) were not seen for metabolic, MSLT or sleep variables. The data indicated that caffeine was effective in producing significant metabolic and sleep effects and that those effects were related. The results were consistent with the interpretation that a chronic decrease in sleep efficiency associated with increased physiological arousal, although producing subjective dysphoria, does not produce a physiological sleep debt. **Key Words:** Sleep—Insomnia—Caffeine—Sleep deprivation—Sleep disorders—Metabolism.

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The development of effective treatment for psychophysiological (DSM-III primary) insomnia depends upon understanding the underlying cause of the disorder. There are two major theoretical explanations of persistent psychophysiological insomnia. Some investigators hypothesize that insomnia is the product of internalization of emotions (psychological activation) and that the attendant emotional arousal leads to cognitive hyperactivity and poor sleep. Others believe that hyperarousal (physiological activation) is a direct physiological cause of insomnia.

Many studies support the concept of greater physiological activation in insomniacs. In a classic study, Monroe (1) found significantly increased physiological activation (increased rectal temperature, heart rate, basal skin resistance and phasic vasoconstrictions) 30 minutes before and during sleep in insomniacs as compared to normal sleepers. Careful studies of sleep-onset insomniacs (2,3) have shown that prior to sleep onset, patients with sleep-onset insomnia had increased frontalis (4) and mentalis electromyogram (EMG), increased heart rate (5), increased finger temperature and

more beta and less alpha frequencies in their electroencephalograms (EEGs). At sleep onset, the physiological parameters normalized except for the EEG changes, which were seen during stage 1 sleep and again during rapid eye movement (REM) sleep. In a study that included sleep maintenance insomniacs, the all-night heart rate elevation but not the increased vasoconstrictions reported by Monroe (1) were replicated (6). Significantly elevated body temperature has been reported in some studies of poor sleepers (1,7,8) but not in other studies (9-11). Poor sleepers have increased secretion of corticosteroids (7,11,12) and adrenaline (7,12) compared with good sleepers in most, but not all, studies (13). The inconsistent results in some of these physiological activation studies may indicate that physiological activation is not a major factor in at least some insomniacs (14) or that wide variability and small sample sizes may make it difficult to show clear physiological differences in comparisons of groups of subjects. It is also possible that the involved physiological system(s) differ from patient to patient and that a global measure, such as whole-body O<sub>2</sub> use, would more consistently show differences.

The experimental production of emotional or physiological stress at sleep onset in normal sleepers would be expected to produce insomnia. However, studies that have placed various stressors before sleep have

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usually not produced clinically significant sleep disturbance or reports of insomnia (15–18). This may be due to ineffective stimuli that have decreased beyond an active range by the time subjects were in bed or that were not significant enough to have an impact upon sleep. It is also probable that individual differences in response to a given stress play a large role in producing a somatic stress reaction and attendant insomnia (19).

Karacan et al. (20,21) and Okuma et al. (22) have suggested that insomnia can be modeled in normal subjects by the administration of caffeine. Caffeine at doses of 300–400 mg given at or near sleep onset resulted in 30–80-minute reductions in total sleep time (21,23). Sleep-onset or middle-of-night insomnia can be produced by varying the time of caffeine administration (21), and the resulting insomnia can be reversed by benzodiazepines (22). Studies have documented the fact that caffeine disturbs sleep in a clear dose-related fashion (20,21,23–25). However, effects on performance, mood and alertness on the day following nocturnal caffeine administration before sleep or on nights or days following complete metabolism of the caffeine are unknown.

A relationship between caffeine and insomnia has also been reported in clinic populations. Caffeinism is itself a common cause of insomnia in patients seen in sleep disorders centers (26). Caffeine use is higher in poor sleepers than in good sleepers (27), and insomniacs who decreased their caffeine consumption all decreased their poor sleep nights from an average of 4.8 to 1.2 nights per week (28).

The use of caffeine to model insomnia has several significant advantages: a) repeated measures studies of normal subjects can be designed to eliminate variability problems seen in insomniac populations (29); b) discrete beginning and end points can be identified; c) weight, age, sex and psychological status can be controlled; and d) caffeine administration results in clear acute physiological effects, including increased heart rate (30,31), blood pressure (30,32,33), respiratory rate (30) and increased epinephrine and norepinephrine secretion (30). Time and dose linked increases in metabolic rate after caffeine use have been consistently found in many daytime studies (34–41). One study has shown that 300 mg of caffeine at bedtime resulted in an increase in oxygen consumption for 5 hours during sleep after a single administration (42). Two studies (42,43) have reported a consistent, dose-related 0.2–0.4°F increase in rectal temperature throughout a night of sleep following 260–390 mg of caffeine. The effects of chronic caffeine use on metabolism have not been directly studied, but it has been shown that metabolic rates changed to the same extent in groups of regular caffeine users (300 mg per day) as compared to infrequent caffeine users (50 mg per day) when both groups

were given a standard 300-mg dose (34). These data suggest that significant caffeine use during the day would increase metabolism and that these effects would be chronic. The pharmacokinetic properties of caffeine do not change with chronic use (44), but one study (45) has shown that tolerance develops in 1–4 days to effects in increasing blood pressure, heart rate, plasma epinephrine and urinary catecholamine. Unfortunately, laboratory studies relating caffeine to sleep have primarily examined the acute effect of caffeine administered shortly before attempted sleep onset (20–24). The two exceptions, a questionnaire study that found no significant effect on sleep of a 150-mg dose of caffeine given at bedtime in a group of regular caffeine users (46) and a note in one study that the effects of caffeine administered on four nights did not differ (24), are difficult to interpret due to lack of detail.

If caffeine can successfully be used to model insomnia, then individuals given caffeine should demonstrate both nocturnal sleep and residual daytime deficits that are similar to those seen in insomniacs. The cumulative partial sleep deprivation that should arise from chronic insomnia would be predicted to result in daytime sleepiness, but studies have consistently found that insomniacs are not any sleepier than normal controls on multiple sleep latency tests (MSLTs) (9,47–49) under normal conditions or after sleep loss (50,51) and may actually have longer MSLT latencies (52–54). Studies comparing daytime performance in insomniacs to normal controls have not found differences on tests that are sensitive to sleep loss (8,9,47,53,55). Studies have found that insomniacs made more errors on a line-tracing task (53), produced fewer responses in a word category test (9) and performed worse on the Romberg (balance) test (55). These results may be interpreted as insomniacs doing worse on tests where too much arousal reduces steadiness or blocks higher order associates. These studies as well as patient reports that insomniacs are fatigued or “washed out” during the day, have led investigators to hypothesize that standard sleep and sleep-loss tests are confounded in that they “simultaneously measure sleep need and hyperarousal, which is interfering with sleep onset” (52). This concept is supported by the fact that these studies (47,52,53,56) report significant negative correlations between total sleep at night and MSLT values on the next day. Possible explanations of the performance data include not only the “hyperarousal” hypothesis, but also the simple hypothesis that these patients have a reduced sleep need or are sleep satiated and have focused on their reduced sleep need in a psychopathologic manner.

The present experiment sought to separate physiological and psychological theories of psychophysiological insomnia by developing a model of insomnia that

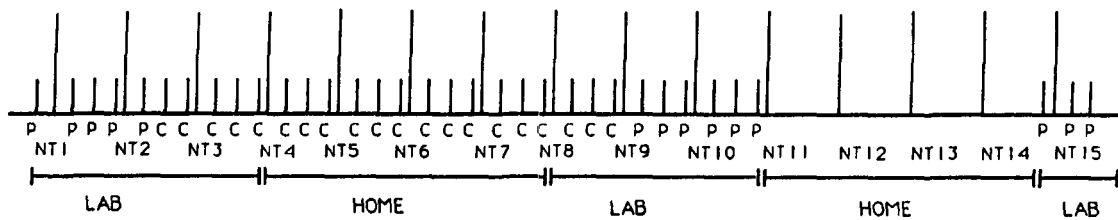


FIG. 1. This study time line indicates nights spent in the laboratory and at home and gives the administration schedule for caffeine (C) and placebo (P).

allows quantification of acute and chronic physiological arousal in normal subjects. It was hypothesized that when metabolism was increased by caffeine, sleep efficiency would decrease. Other symptoms found in insomniacs such as increased MSLT values, subjective fatigue, anxiety and irritability were also predicted. Finally, it was predicted that increased sleepiness, performance loss and EEG rebound effects would be found after caffeine withdrawal. Measurement of these effects would allow an estimate of residual decrement, normally masked by hyperarousal in insomniacs, to be obtained. The sleep-related effects predicted are different from and separable from reported effects of caffeine withdrawal, which include headache, irritation, nervousness, anxiety and dizziness (57).

## METHOD

### Subjects

Subjects were 12 healthy, 18–30-year-old males weighing 140–200 pounds and without significant history of sleeping problems, shiftwork or frequent naps. Potential subjects using more than 250 mg of caffeine or the equivalent per day were excluded. All subjects completed an informed consent and a session of practice on tests before being scheduled for the study.

### Design

After practice, subjects were scheduled for a laboratory adaptation night, which was preceded and followed by additional test practice. The study period, which consisted of 10 consecutive nights with a final baseline night 5 nights after the 10 consecutive nights, is diagramed in Fig. 1. Subjects received pills three times a day throughout the study period. The first five pills that subjects received beginning on the first evening were placebo. Subjects then received 400 mg of caffeine (Eleveine sustained release formulation, Alva-Amco Pharmacal Co., Inc., Chicago, IL, U.S.A.) three times a day for the next 7 nights and days (20 total administrations) and placebo for all remaining periods. Subjects remained at the lab for the first 3 nights and

days, returned to the lab each evening for medication for each of the next 4 nights (but slept at home) and remained in the lab for study nights 8–10 and the following days. Night 15 served as a final baseline night and day. The study normally began on a Thursday night, and sleep and wake times were scheduled according to the subject's habitual bed time and wake time. After awakening in the morning, all subjects followed the same schedule of alternating MSLTs, metabolic observations, performance test blocks, meals and breaks during each day. All subjects received pills at morning awakening, 8 hours later, and 15 hours later (the times were approximately 0800, 1600 and 2300 hours).

All subjects were assigned their own rooms for the course of the study. Each room contained a standard hospital bed and furniture, including a desk with an Apple IIGS computer. Subjects participated in the study in groups of 1–4 individuals. Subjects completed all tests and questionnaires at their individual computer workstations in their rooms under technician observation. Nonstartling procedures, such as calling the subject's name, were used by the technicians to awaken faltering subjects. Meals and breaks were scheduled in another area of the laboratory, which was also under technician observation. Caffeinated beverages were not available.

### Tests

Performance and mood were assessed with a battery of measures, including hand tremor (2-minute insertion of a stylus into a 4-mm opening with percent of side touching time measured), computer modified Williams word memory test of immediate free recall (58), visual vigilance [30 minutes (59)], the MAST letter search task [one, three and five targets (60)], a proof-reading test (10 minutes), subjective sleepiness (10-point analog scale), profile of mood states (POMS) and oral temperature. The tests were administered in repeated batteries. The same test schedule was followed on each day in the laboratory and resulted in each test being repeated 4–5 times each day. For all subjects on all measures except MSLT, performance during continuous operations was automatically scored by the

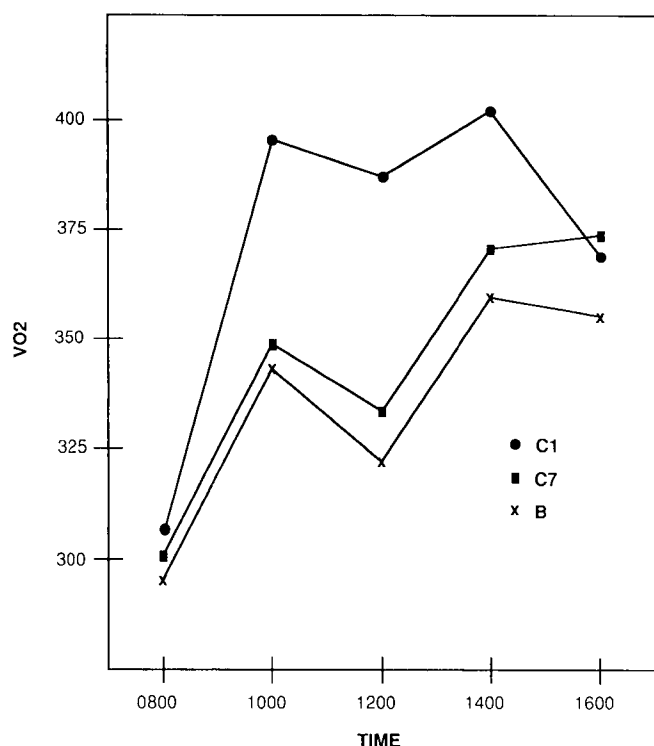


FIG. 2. Metabolic rate, as measured by  $\dot{V}O_2$  across daytime test sessions after baseline (B), acute caffeine (C1) and chronic caffeine (C7) use.

computer and output in a format suitable for statistical analysis.

### MSLT and metabolic observations

The MSLT was performed at 1000, 1200, 1400, 1600 and 2200 hours. The timing of the MSLT differed from the standard in that the final nap was placed at 2200 hours rather than 1800 hours. The 2200 hours time was chosen for this study because the MSLTs were also used as a stabilization period for metabolic observations, which followed immediately. The 1800 hours time closely followed dinner, making metabolic observations less reliable, and the 2200 hours time allowed a metabolic observation relatively close to the nocturnal sleep onset. The MSLT was terminated after 20 minutes with no sleep, after 10 minutes from the appearance of stage 1 sleep, or 1 minute after the appearance of sleep spindles, K-complexes or REMs, whichever came first. Metabolic observations were made immediately upon awakening in the morning and immediately following each MSLT observation during the day. The MSLT was scored for the latency to stage 1 sleep to maximize the sensitivity of the test to the predicted long sleep latencies. Each metabolic observation was performed using a SensorMedics MMC Horizon metabolic cart. Subjects used a mouthpiece

and standard nose clip for each 21-minute metabolic observation. The SensorMedics MMC metabolic cart was programmed to provide 3-minute averages of  $\dot{V}T$  = tidal volume (liters per breath),  $\dot{V}O_2$  (STPD) = oxygen consumption (liters per minute),  $\dot{V}CO_2$  (STPD) = carbon dioxide production (liters per minute), RQ = respiratory quotient, frequency (breaths per minute), and time. The data were output to the laboratory computer for storage and analysis following each metabolic observation (61). Subjects were requested not to move, read or be otherwise occupied during metabolic observations, and EEG was recorded during each observation so that wakefulness could be assured.

### EEG recordings

Four-channel sleep recordings (LE-A2, RE-A2, C3-A2, OZ-A1) were made during nocturnal sleep periods and MSLT evaluations.

### Data analyses

Initial baseline and final withdrawal values [night (NT) 15] were compared for all variables. Significant differences were not found for sleep, MSLT or metabolic values, and these values were therefore averaged for a baseline condition. Similarly, withdrawal values were compared to baseline values and were averaged with baseline values when differences were not apparent (metabolic data). Repeated measures analyses of variance were performed with effects for baseline, early caffeine (NT 1 and the following day), chronic caffeine (NT 9 and the preceding day) and, usually, withdrawal (NT 10 and the preceding day). For measures that were repeated across each day—MSLT, performance and mood observations—a term for time of test (3–5 df) was added to the ANOVA. Pairwise comparisons were performed with the Newman-Keuls test at the 0.05 level, using the Greenhouse-Geisser degrees of freedom. All reported results in the text will refer to statistically significant differences unless noted otherwise. Results on the many performance tests were similar. Therefore, only data from MSLT, vigilance, tremor, short-term memory, MAST, proofreading and the POMS subscales will be presented in this report.

## RESULTS

### Subjects

The subjects selected for this study were  $20.6 \pm 1.5$  years of age,  $170 \pm 23$  pounds, and consumed  $86 \pm 74$  mg of caffeine per day prior to entry into the study.

Table 1. Nocturnal baseline and recovery sleep

	Baseline	Early caffeine	Late caffeine	Withdrawal	F	p	Difference
Total sleep time	445.	367.	424.	429.	8.42	0.000	C1 < All
% Stage 1	10.7	13.4	13.3	12.2	2.08	0.121	
% Stage 2	45.3	37.2	43.1	42.6	4.62	0.008	C1 < All
% Stage 3	6.2	4.8	6.1	5.7	1.83	0.160	
% Stage 4	15.2	10.9	11.9	16.8	7.04	0.001	C1 = C7 < BL = WDL
% Stage REM	18.7	18.5	19.5	17.2	0.98	0.413	
% Stage movement	0.7	0.6	0.8	0.7	0.36	0.780	
Sleep latency	13.8	40.2	28.4	20.7	4.51	0.009	C1 > WDL = BL
Latency to REM	81.2	74.2	88.7	87.5	0.59	0.623	
Wake time	13.8	62.2	21.9	20.2	4.36	0.011	C1 > All
Stage changes	119.	121.	129.	124.	0.76	0.523	
Time in bed	472.	470.	474.	470.	0.29	0.826	
Sleep efficiency	94.2	78.8	89.6	91.3	7.99	0.000	C1 < All
# of wakes	1.0	2.3	1.3	1.4	3.39	0.029	C1 > All
EEG arousals	70.	67.	78.	66.	1.46	0.243	
Arousal index	9.1	11.0	10.7	8.7	4.02	0.015	C1 = C7 > BL = WDL

### Sleep data

Nocturnal sleep stage data are presented in Table 1. Significant group differences indicative of poor sleep were seen during caffeine administration. As expected, acute caffeine administration resulted in decreased total sleep time and increased sleep latency. Additionally, stage 2 and stage 4 sleep were significantly reduced and awakenings and brief arousals were increased. On the final caffeine administration night, the degree of sleep disturbance was decreased compared to the acute caffeine condition, but stage 4 sleep was still significantly reduced in comparison to baseline. Brief arousals were still significantly elevated. With an average sleep latency of 28 minutes and a sleep efficiency below 90%, these young adults could still receive a tentative diagnosis of insomnia. Sleep on the withdrawal night (which began 24 hours after the final administration of caffeine) did not differ significantly from baseline for any sleep measure.

### Metabolic data

For the metabolic data, no significant differences were found among the initial baseline, final baseline and withdrawal day values. Therefore, all of these data were averaged into a baseline condition for comparison with the caffeine conditions. In the ANOVA that compared the six daily metabolic observations, a significant condition by time interaction was found ( $F_{10,90} = 2.78$ ;  $p = 0.005$ ). The metabolic data are plotted in Fig. 2. The interaction reflected the fact that metabolic rates did not differ before caffeine administration (0800 hours), that metabolic rate on the initial caffeine day was significantly elevated 2, 4 and 6 hours after caffeine administration and that metabolic rate was not significantly elevated 8 hours after caffeine administra-

tion (1600 and 2300 hours). Metabolic rates on the seventh day of caffeine administration differed significantly from the first day of caffeine administration, but not from baseline for the same observation periods. Metabolic rate was increased an average of 12% over the baseline level during the 8 hours after caffeine administration on the first caffeine day and an average of 3% over the baseline value on the final day of administration. Within-subjects correlations across the study showed that all subjects except one had a negative correlation between metabolic rate at bedtime and sleep efficiency for the sleep period that followed (average  $Rho = -0.58$ ; binomial probability = 0.0059). Within-subjects correlations between each paired MSLT value and the following average  $\dot{V}O_2$  value from the metabolic observation showed that all 12 subjects had positive correlations between sleep latency and metabolic rate (binomial probability = 0.0002). However, the level of those correlations was generally low (average  $r = 0.23$ ). Between-subjects Pearson correlations between change in metabolic rate and sleep efficiency from baseline to the first caffeine night and last caffeine night were of borderline statistical significance ( $r_{sc1 \times mc1} = 0.50$ ,  $p < 0.1$ ;  $r_{sc7 \times mc7} = 0.67$ ,  $p < 0.05$ ). Metabolic rate change from baseline was more highly correlated from the first to last caffeine night than was change in sleep efficiency over the same period ( $r_{mc1 \times mc7} = 0.822$ ,  $p < 0.01$ ;  $r_{sc1 \times sc7} = 0.38$ ,  $p = ns$ ).

### MMPI and POMS data

The entire MMPI was administered before caffeine use, at the end of the caffeine administration period and on the final baseline day. Values from the baseline days were averaged for comparison to the caffeine values, and the data are presented in Table 2. All the

**Table 2.** *MMPI values from baseline and after chronic caffeine use*

Scale	Baseline	Caffeine	F	p
Hypochondriasis (Hs)	47	48	0.12	0.73
Depression (D)	45	46	0.79	0.39
Hysteria (Hy)	52	53	0.58	0.46
Psychopathic deviate (Pd)	58	59	0.04	0.84
Masculinity/femininity (Mf)	63	61	2.93	0.11
Paranoia (Pa)	56	57	0.16	0.69
Psychasthenia (Pt)	53	58	5.64	0.03
Schizophrenia (Sc)	62	67	1.95	0.19
Hypomania (Ma)	74	74	0.02	0.87
Social introversion (Si)	43	45	0.92	0.35

MMPI values remained characteristic of young adults, but there was movement toward increased pathology on all the clinical scales except Mf, and the change was statistically significant for the Pt (anxiety) scale.

Data from the Profile of Mood States suggested increasing dysphoria as caffeine administration progressed (see Table 3). Significant main effects for Condition were found for all six POMS scales. Two patterns were evident. For the scales Vigor and Tension (anxiety), initial caffeine administration resulted in an immediate significant increase followed by a decrease as caffeine administration continued (significant for Vigor). For the scales Fatigue, Confusion, Depression and Anger, incremental increases were seen as caffeine ad-

ministration continued and withdrawal occurred. For Depression and Confusion, the withdrawal values were significantly greater than all other observations. Values in the late Caffeine and Withdrawal conditions were greater than baseline for Fatigue and Anger.

**Subjective sleep evaluation data**

Subjective rating information for the EEG-recorded sleep nights reported earlier can be found in Table 4. The subjective data generally approximate the objective EEG sleep data well. Significant differences were limited to the perception of longer sleep latency, more awakenings, decreased sleep length rating and worse sleep quality on the initial caffeine administration night.

**Psychomotor performance and MSLT data**

Psychomotor tests analyzed included vigilance P(A), hand tremor, MAST, short term memory and proof-reading. On all performance tests, changes across the study were relatively minor. Significant differences were not found for vigilance, tremor or short-term memory, although all measures showed a trend for improved performance throughout caffeine use and a return toward baseline during withdrawal. Significant condition by time interactions were found for the MAST ( $F_{9,99} = 2.16, p < 0.05$ ) and proofreading tests ( $F_{9,99} = 2.43,$

**Table 3.** *Profile of mood states data*

	Baseline	Early caffeine	Late caffeine	Withdrawal	$F_{3,132}$	p	Difference
Fatigue	4.8	5.8	6.8	7.8	4.23	.01	B < C7 B = C1 < WDL
Tension	5.9	10.2	8.6	9.8	9.56	.001	B < all
Depression	3.7	4.1	5.9	8.4	7.84	.001	WDL > all
Anger	4.4	5.7	7.2	8.6	5.05	.005	B < C7 = WDL C1 < WDL
Vigor	15.5	20.1	13.7	13.0	10.89	.001	W = C7 < B < C1
Confusion	4.0	4.3	5.1	6.4	8.42	.001	WDL > all

**Table 4.** *Subjective sleep ratings*

	Baseline	Early caffeine	Late caffeine	Withdrawal	F	p	Difference
Bed time	2342	2339	2343	2348	0.28	0.84	
Wake time	0751	0736	0740	0753	1.09	0.36	
Sleep latency	37.5	55.4	32.0	27.5	1.20	0.32	
Latency rating	4.2	5.8	4.9	4.5	5.12	0.01	C1 > all
# of wakes	1.9	2.9	1.3	1.3	5.00	0.01	C1 > all
Time awake	39.7	75.4	20.5	25.4	2.06	0.12	
Sleep length	7.4	6.4	7.1	7.4	3.33	0.03	C1 < all
Sleep length rating	2.1	2.6	2.4	2.1	4.27	0.01	C1 > all
Sleep depth	1.7	2.2	2.0	2.0	2.01	0.13	
Sleep quality	2.1	3.3	2.6	2.6	4.42	0.01	C1 > all
AM feeling	3.8	4.0	4.2	4.5	0.51	0.67	
Log time awake	2.5	3.2	2.2	1.9	1.78	0.17	
Log latency	2.9	3.6	3.1	3.0	3.97	0.01	C1 > all

$p < 0.05$ ). Pairwise comparisons indicated that for the MAST, performance was improved during initial caffeine use at the final evening test point as compared to all other conditions. For the proofreading test, performance was improved during chronic caffeine condition at the late afternoon test point as compared to all other conditions.

Analysis of the MSLT data revealed that objective alertness was significantly improved throughout caffeine administration as compared to baseline and withdrawal, which did not differ ( $F_{3,165} = 39.29$ ,  $p < 0.0001$ ). Mean nap latencies from the individual MSLT observations can be found in Table 5. The mean latency after early caffeine use was significantly longer than the latency after chronic caffeine use. Respective means for baseline, early caffeine, late caffeine and withdrawal were 10.7, 17.9, 13.4 and 11.3 minutes. Similar results were found when data from only the first four naps (1000, 1200, 1400 and 1600 hours) were analyzed.

## DISCUSSION

In this study, it was predicted that caffeine would produce chronic physiological arousal, defined as a significant increase in metabolic rate as measured by  $\dot{V}O_2$ . It was also predicted that poor sleep and the symptoms commonly reported by insomniacs would be produced. Finally, it was predicted that chronic poor sleep would result in the accumulation of deficits that could be measured during the withdrawal period.

The results showed that the administration of caffeine was successful in significantly increasing metabolic rate and in reducing sleep efficiency to levels commonly associated with "insomnia" during initial administration. In addition to the related changes in metabolic rate and sleep efficiency, many similarities were found between symptoms reported by insomniacs and the subjects in the present study. In addition to poor sleep, it has generally been established that many patients with insomnia will: a) report daytime fatigue or dysphoria; b) have normal or longer than normal MSLT values; c) report increased stress; d) possibly have abnormal MMPI values; e) subjectively misperceive their sleep process; and f) have few notable differences from normals on psychomotor performance tasks.

The POMS rating data from this study show consistent increases in dysphoria during the caffeine administration. The mood changes were relatively small but consistent and significant on all POMS subscales during the study. The POMS data describe a reasonable set of somatic complaints that can typically be found in patients with insomnia. Fatigue, confusion, anger and depression all increased in a linear fashion during caffeine administration. Vigor and tension (anxiety)

**Table 5.** Mean and (standard deviation) of multiple sleep latency test values across the day

Time	Baseline	Early caffeine	Late caffeine	Withdrawal
10.00	8.6 (7.0)	14.3 (6.7)	8.7 (6.7)	6.8 (4.4)
12.00	9.6 (5.9)	18.9 (3.0)	13.9 (6.8)	10.3 (5.1)
14.00	11.8 (4.8)	17.4 (3.5)	13.6 (6.2)	10.8 (4.4)
16.00	12.4 (6.8)	18.6 (3.0)	15.8 (5.6)	13.2 (3.4)
22.00	11.4 (5.9)	20.0 (.04)	14.8 (5.8)	15.4 (4.6)
Mean	10.7	17.8	13.4	11.3

increased with initial caffeine administration and then decreased in what could be a tolerance, or adaptation, effect. These changes might also reflect adjustment to an increased level of arousal. Withdrawal from caffeine was also initially reported as a negative event in that all POMS scales continued to move in a negative direction. Because the first withdrawal day was preceded by caffeine-degraded sleep in addition to withdrawal from caffeine, increasingly negative ratings would be expected. These reported effects are not simply representative of subjects becoming disgruntled or tired of the experiment because, in all cases, data from a final baseline day about 1 week after withdrawal did not differ from the baseline values (and were averaged with the baseline values for all reported comparisons).

MSLT values were very representative of what might occur in a patient with chronic insomnia. With initial administration of caffeine, the mean for the MSLT approached 20 minutes (the maximum). After 1 week of caffeine use, MSLT latencies had decreased from the 20-minute range but still remained significantly elevated from baseline levels. Such MSLT latencies, when associated with subjective vigor ratings significantly lower than baseline, suggest dysphoria commonly reported by insomniacs, who frequently show somewhat elevated MSLT values while complaining of fatigue (52–54). MSLT values immediately returned to baseline on the first withdrawal day, which began about 9 hours after the last caffeine administration. The immediate MSLT return is in contrast to the POMS values, which continued to move to more extreme negative values on this day. This suggests either that the arousal effects of caffeine had passed but that psychological withdrawal remained or that the subjective state of arousal had changed as a function of caffeine use. MSLT values also remained at the same baseline level on the following day. This indicates that the data from the initial withdrawal day were not dependent upon residual caffeine in the system and strengthen the contention that sleep rebounds did not exist.

After 1 week of caffeine use, MMPI values for the group consistently moved in the pathological direction by small amounts. The one scale that increased sig-

nificantly, Pt, did so only by 5 points and remained within 1 standard deviation of the norm. However, if one looks at the individual data, three subjects had major increases in Pt (10–15 points) and two subjects ended up at or in the pathological range at the end of the caffeine condition. The subject with the largest increase on the Pt scale also had a large decrease in sleep efficiency (range 49–77) and a large increase in metabolic rate (range 13–16% while using caffeine). Additionally, one subject moved into the pathological range on Pa after caffeine and two subjects moved into the pathological range on SC after caffeine. The MMPI and POMS data together suggest that simple physiological activation over a 1-week period can result in changes in reported mood and personality. This implies that personality types common in insomnia can develop as a function of hyperarousal rather than causing hyperarousal.

The data from this study do not indicate that participants had more of a tendency to misperceive their sleep process when using caffeine than when not using caffeine. If it is hypothesized that a) physiological arousal increases or alters mentation so that mentation during sleep onset periods is more similar to waking mentation or b) that people when lying awake spontaneously begin to dwell on events that make the perception of the point of sleep more difficult, it would be expected that the subjects in this experiment would also misperceive. To examine this issue in more detail, subjective sleep rating data from the three subjects who had the greatest changes on the Pt scale of the MMPI, the three subjects who had the greatest changes in metabolic rate and the three subjects who had the greatest changes in EEG sleep were examined separately. It was found that the subjects who had large PT changes overestimated their sleep onset latency by 7 minutes on baseline nights (9 vs. 16 minutes) and by 13 minutes on caffeine nights (39 vs. 52 minutes). The three subjects who had the greatest change in metabolic rate overestimated their sleep onset latency by 2 minutes on baseline nights (12 vs. 14 minutes) and by 13 minutes on caffeine nights (21 vs. 34 minutes). The three subjects who had the greatest change in EEG sleep overestimated their sleep onset latency by 9 minutes on baseline nights (14 vs. 23 minutes) and by 10 minutes on caffeine nights (42 vs. 52 minutes). The number of extreme subjects is probably too small to do meaningful analyses, but neither the MMPI data, the metabolic data, nor the EEG extreme data suggest a strong tendency for subjects to overestimate sleep parameters.

Caffeine did not have a significant impact on any psychomotor variable. Three of the tests—vigilance, MAST and proofreading—measured sensitivity relatively unbiased by motivation [ $P(A)$ ] and did not change as a function of caffeine use. Similarly, correct response

productivity did not change. These present data agree with previous studies, which have shown little difference in the performance of insomniacs as compared to normals (8,9,47,53,55).

One may hypothesize that caffeine produces insomnia by several possible mechanisms. If caffeine produces insomnia by its direct effect on metabolic rate, then there should be significant correlations between change in metabolic rate and change in sleep. That there were positive and significant relationships between nocturnal metabolic rates and sleep latencies and between MSLT values and metabolic rates is important. Unfortunately, the low level of correlation between metabolic rate and sleep latency is problematic. There was a tendency for individual subjects who had low correlations between MSLT and metabolic rate to have a large number of 20-minute (maximum) sleep latencies. This operational issue certainly limited the possibility of finding correlations at higher levels of alertness and metabolic rate. When the individual metabolic/MSLT correlations from the five subjects who had eight or fewer 20-minute sleep latencies were examined, the median correlation increased to  $r = 0.34$ , but, even at this level, less than 12% of the variance is accounted.

The data indicate that there was adaptation to the metabolic and insomnia-producing effects of caffeine over the 7 days. However, on the final caffeine day, metabolic values were still increased about 3% above baseline values, and sleep efficiency, though within 2 standard deviations of normal for the age group, was still below 90%. It can be argued that the development of some tolerance in terms of both metabolic and sleep effects over the course of caffeine administration decreased the effects of the insomnia in producing residual sleep deficits. To present a more clear picture of the amount of sleep obtained during the period of caffeine administration, subjective reports of sleep latency and sleep efficiency over the entire period (i.e. both lab and home nights) of caffeine administration were examined. In general, subjects tended to overestimate both their sleep latency (4–15 minutes) and their sleep efficiency (0–3%) on lab nights. Over the course of the seven lab and nonlab caffeine administration nights, subjects estimated that they fell asleep in a median of 44 minutes (range 20–74) and had a mean sleep efficiency of 86% (range 81–89%). Taking into account an overestimation of sleep latency and sleep efficiency, these numbers indicate that, on the average, participants were very near the standard criterion of a sleep latency of 30 minutes or a sleep efficiency of 85% typically used to define an individual as an insomniac. However, as these data are representations of central tendency, some subjects must have slept better than these values indicated. If there were an experimental



tolerance effect, one would have expected all measures to have moved to baseline levels by NT 9. In the mood data, four of the six scales (all except tension and vigor) continued to move in the negative direction during caffeine administration. This suggests continuing impact rather than adaptation.

The data from this study are consistent with the view that people who have an increased level of arousal, which may be associated with psychophysiological factors, general anxiety or the use of stimulants such as caffeine, tend to have difficulty sleeping secondary to their heightened arousal. Such heightened arousal may be transitory or chronic. The hyperarousal may directly cause both sleeping problems and dysphoric mood, including fatigue. Some other types of insomnia, such as phase shift insomnia, may also be directly related to an inappropriately high level of arousal at the time of the sleep attempt. However, other physiological pathologies such as chronic pain, sleep apnea or leg movements, which may result in a report of insomnia, clearly are not cases of hyperarousal. One would expect patients with an identifiable cause of poor sleep, such as sleep apnea, to have normal or shorter than normal MSLT latencies, depending upon the degree of sleep disturbance. However, when patients have longer than normal MSLT values (for example, latencies > 15 minutes), it may be an indicator that these patients are excessively aroused.

There were marked individual differences in this study in the impact of caffeine on sleep in terms of both acute and chronic responses. Large response variability may be due to individual sensitivity to caffeine or sturdiness of the sleep response in the face of the caffeine manipulation. Independent variability of these parameters presents the opportunity to differentiate them. However, the small number of subjects in the current study did not allow the development of strong potential interrelationships.

Can the effects reported in this study be entirely secondary to the psychoactive effects of caffeine and therefore irrelevant to our knowledge of insomnia? In the end, of course, one must evaluate any model by its ability to correctly describe the phenomena being modeled and lead to new conclusions or testable hypotheses. The group data presented here certainly suggest that it is possible to produce poor sleep in a relatively heterogeneous group of normal young adults with caffeine. The poor sleep produced does not appear to be different from that seen in insomniacs, and accompanying changes in MSLT, mood, personality and psychomotor performance support findings in studies of real insomniacs. It is possible that the poor sleep of insomniacs is different in some way from the poor sleep produced by caffeine in this study. It is also possible that some of the subjective response measures reported

in this study reflect caffeine use or withdrawal more than physiological activation or sleep. These possibilities are unlikely because the findings are similar to those seen in patients with insomnia. However, this question can only be answered in fact by future tests of the linkage between physiological arousal and insomnia. The current results do explain data and lead to testable hypotheses based upon the tenant that many of the symptoms of insomnia may be a direct result of hyperarousal or inappropriate arousal. For example, if insomnia is more related to arousal than to insufficient sleep, then a treatment strategy that decreases sleep [sleep restriction therapy (62)] will successfully treat insomnia, not because it treats a behavioral or circadian rhythm deficit, but because the sleep restriction results in the accumulation of a small sleep debt that both increases sleep efficiency and decreases arousal level. If insomnia really entailed a sleep deficit, sleep restriction therapy would make the insomnia significantly worse. Thus, hyperarousal would predict that any manipulation that decreases overall arousal level would decrease the severity of insomnia and that any manipulation that increases arousal level would increase the severity of insomnia.

A core belief in dealing with insomniacs is that their sleep is in some manner less restorative. Consequently, insomniacs suffer from daytime compromise. Data from chronic partial sleep loss studies in normal sleepers indicate that multiple nights of sleep limited to 5 hours or less are required to produce physiological consequences (63). Measurable consequences were difficult to produce in normal sleepers limited to 5.5 hours per night for a period of months (64,65), and these chronic total sleep times are less than those commonly found in insomniacs. It is nonetheless possible that sleep with an aroused physiological system is different from sleep with a less aroused physiological system (66). The existence of a chronic sleep debt in insomniacs cannot be measured in insomniacs because they typically cannot be tested without the insomnia. The withdrawal condition in this experiment provided a direct attempt to determine whether a period of poor sleep associated with increased arousal would result in the accumulation of measurable changes in sleep or alertness. Although it was hypothesized that the period of poor sleep would result in rebounds, the data indicate that the withdrawal from caffeine was not associated with either EEG sleep rebounds or increased daytime sleepiness, as measured by the MSLT. One might contend that 7 days form an insufficient period for significant deficits to accumulate, but the lack of trends after 7 days seems more indicative of a minor or nonexistent effect. One could also criticize the current study for having too short an acute withdrawal period. However, the fact is that MSLT values were at baseline levels on

two consecutive days following the last (evening) dose of caffeine. Similarly, the nocturnal sleep 24 hours after caffeine administration, at a time when only about 3% of the last caffeine dose remained, was also at baseline levels. The absence of MSLT and sleep rebound effects leads one to hypothesize that patients with insomnia have sleep that is equally restorative to patients without insomnia and therefore have no accumulated sleep debt. If such were the case, one would predict that insomniacs would have MSLT values that would be in the normal range, as they are. The effects that remain to be explained are the daytime fatigue and dysphoria symptoms, which have traditionally been attributed to poor sleep or to personality. The present data suggest a third possible explanation. It is possible that the fatigue that insomniacs report is secondary to chronic hyperarousal. It was found in the current study that subjective vigor was significantly increased at the beginning of caffeine administration. However, by the final day of caffeine administration, subjective vigor was significantly below baseline levels, although MSLT values were still significantly greater than baseline values. The implication of these data is that measurable physiological arousal continues chronically, but the perception of the arousal changes from a sensation of increased energy to a sensation of uncomfortable inability to rest or relax. Obviously, the key component in this scenario is not sleep loss per se, but rather degree and duration of hyperarousal. It is reasonable to envision a continuum of arousal set points ranging from the hypoarousal of hypersomnolence at one extreme to the hyperarousal of insomnia at the other extreme. This suggests that many insomnias are disorders of hyperarousal rather than sleep disorders.

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