

Caffeine Eliminates Psychomotor Vigilance Deficits from Sleep Inertia

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Study Objectives: This study sought to establish the effects of caffeine on sleep inertia, which is the ubiquitous phenomenon of cognitive performance impairment, grogginess and tendency to return to sleep immediately after awakening.

Design: 28 normal adult volunteers were administered sustained low-dose caffeine or placebo (randomized double-blind) during the last 66 hours of an 88-hour period of extended wakefulness that included seven 2-hour naps during which polysomnographical recordings were made. Every 2 hours of wakefulness, and immediately after abrupt awakening from the naps, psychomotor vigilance performance was tested.

Setting: N/A

Participants: N/A

Interventions: N/A

Measurements and Results: In the placebo condition, sleep inertia was manifested as significantly impaired psychomotor vigilance upon awakening from the naps. This impairment was absent in the caffeine condition. Caffeine had only modest effects on nap sleep.

Conclusions: Caffeine was efficacious in overcoming sleep inertia. This suggests a reason for the popularity of caffeine-containing beverages after awakening. Caffeine's main mechanism of action on the central nervous system is antagonism of adenosine receptors. Thus, increased adenosine in the brain upon awakening may be the cause of sleep inertia.

Key words: Sleep inertia; awakening; caffeine; adenosine; sleep deprivation; nap sleep; function of sleep

INTRODUCTION

THE NEUROBIOLOGICAL BASIS OF SLEEP INERTIA,¹ WHICH REFERS TO THE COGNITIVE PERFORMANCE IMPAIRMENT, GROGGINESS AND TENDENCY TO RETURN TO SLEEP IMMEDIATELY AFTER AWAKENING² IS UNKNOWN. Documented cognitive deficits due to sleep inertia include simple and complex reaction time, complex simulation, letter cancellation, logical reasoning, mental arithmetic, vigilance, and memory—in addition to confusion and disorientation—as reviewed by Dinges in 1990.³ Sleep inertia appears to be worse under sleep-loss conditions^{4,5,6} and to vary in magnitude and duration with circadian phase.^{4,7} Evidence suggests that sleep inertia may be associated with the sleep stage at the end of sleep^{8,9} as well as the overall depth of sleep and the intensity of non-REM sleep.^{4,10,11,12}

Sleep inertia is particularly problematic and potentially dangerous in operational settings^{13,14} in which a high level of performance is required during the one to two hours after awakening.^{15,16} Countermeasures could provide insight into the mechanisms underlying sleep inertia. The present study is the first to employ a pharmacological approach to this end: sustained low-dose caffeine administration. Specifically, we investigated the effects of caffeine on sleep inertia under sleep-loss conditions.

METHODS

Experimental Design

In a laboratory experiment involving sleep restriction with

continuous monitoring, normal healthy subjects with a history of moderate caffeine intake were studied. Subjects did not use any alcohol, tobacco, and/or medications in the two weeks before and the 10 days during the experiment. Subjects also refrained from caffeine intake (except as per experimental condition outlined below). After one adaptation day and two baseline days in the laboratory, subjects underwent 88 hours of extended wakefulness with a total of seven two-hour naps scheduled to occur at 12-hour intervals. Subjects were randomized to receive either sustained low-dose caffeine (0.3 mg/kg per hour) or placebo (double-blind) in the last 66 hours of the 88-hour extended wakefulness period except during naps. Every two hours of wakefulness, and immediately after abrupt awakening from the naps during sleep inertia, neurobehavioral performance was tested.

Subjects and Procedures

This laboratory study was approved by the Institutional Review Board of the University of Pennsylvania. Written informed consent was obtained from all subjects. Twenty-eight normal healthy subjects (all male; mean age 29 years, range 21–47 years) with a history of moderate caffeine intake participated in the study. All subjects were screened using a medical, psychiatric, and sleep/wake history, as well as physical and laboratory examinations. Subjects did not use any caffeine, alcohol, tobacco, and/or medications in the two weeks before the experiment, as verified by means of blood and urine screens and questionnaires. Caffeine withdrawal effects usually last no longer than one week.^{17,18} None of the subjects reported any caffeine withdrawal effects.

The laboratory experiment began with one adaptation day and two baseline days with bedtimes from 23:30 until 07:30. Subsequently, subjects underwent 88 hours of extended wakefulness with a total of seven two-hour naps scheduled every 12 hours, from 14:45 until 16:45 and from 02:45 until 04:45. Subjects were awakened from the naps abruptly by a staff mem-

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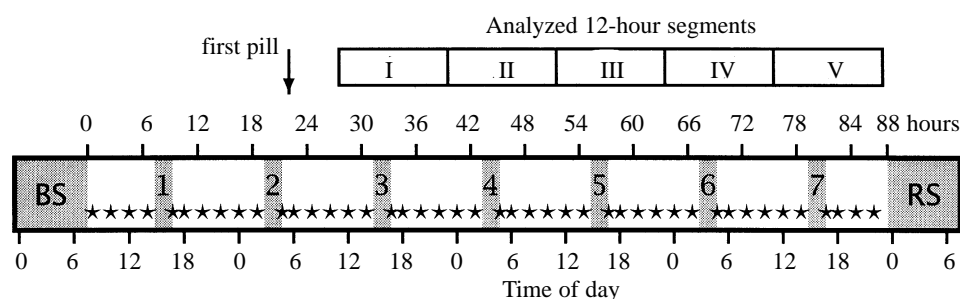


Figure 1—Timeline diagram of the study protocol. Gray areas display sleep periods (the last 8-hour baseline sleep on the left, seven 2-hour naps, and the first 8-hour recovery sleep on the right). Baseline sleep (BS) took place from 23:30 until 07:30, naps (numbered gray bars) were scheduled every 12 hours from 14:45 until 16:45 and from 02:45 until 04:45, and recovery sleep (RS) started at 23:30 after 88 hours of extended wakefulness. Time of day is shown on the bottom of the diagram, and hours of extended wakefulness (including the time spent napping) are shown on the top. Starting 22 hours into the 88-hour extended wakefulness period (as indicated with the arrow above the diagram), subjects received a pill of 0.3 mg/kg caffeine ($n=15$) or placebo ($n=13$) every hour except during naps. Neurobehavioral performance testing (marked with stars in the diagram) began at 08:00 after the last baseline sleep, and occurred every 2 hours except during naps, as well as within 5 minutes after abrupt awakening from each nap. Analyses focused on the consecutive 12-hour segments of the experiment around each of the last five naps (i.e., naps 3 through 7), which involved differential pharmacological conditions. Each of these 12-hour segments (indicated by boxes marked with Roman numerals on the top of the diagram) consisted of two performance test bouts preceding a nap, and four performance test bouts following a nap.

ber calling their names loudly. At times when no nap sleep was scheduled, subjects were kept awake under continuous behavioral monitoring. They were allowed to read, watch movies, and interact with laboratory staff to help them stay awake, but no vigorous activities were permitted.

Starting 22 hours into the 88-hour period of extended wakefulness (i.e., 45 minutes after the second nap), subjects received either 0.3 mg/kg caffeine ($n=15$) or placebo ($n=13$) in a pill every hour except during naps. Thus, subjects received sustained low-dose caffeine equivalent to about a quarter cup of coffee per hour¹⁹ or placebo (randomized double-blind) for 66 hours, but they were led to believe that the content of each pill varied randomly between placebo and caffeine. At 1.5-hour intervals on average, blood samples were taken via an indwelling intravenous catheter for assessment of blood plasma concentrations of caffeine (Emit assay, Syva Company). Blood plasma concentrations for 2 of the 15 subjects in the caffeine condition were missing. After the 88-hour extended wakefulness period, subjects stayed in the laboratory for three recovery days. The laboratory was maintained in less than 50 lux of light at all times. During scheduled sleep times, all lights were turned off (less than 1 lux). A timeline diagram of the study design is shown in Figure 1.

Recordings and Analyses

Starting at 08:00 in the first hour of extended wakefulness, and then every two hours except during naps, subjects' neurobehavioral performance was tested on a 30-minute computerized assessment battery. The battery included a 10-minute high-load psychomotor vigilance task²⁰ starting five minutes after the beginning of testing. For this validated task, which has been shown to be sensitive to sleepiness and performance deficits,^{21,22,23,24} number of lapses (reaction times longer than 500 ms), average of the 10% fastest reaction times, and average of the reciprocal of the 10% slowest reaction times were analyzed. After performance testing, subjects filled out a 20-item survey of symptomatic experiences (e.g., headache, irritability), which revealed no significant differences between the caffeine and

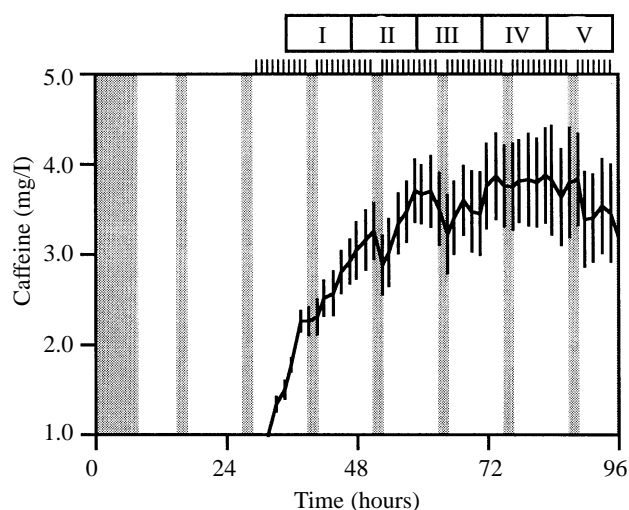


Figure 2—Blood plasma concentrations of caffeine. Means (in mg/l) and standard errors of the mean (vertical bars) are shown for 13 subjects. They received 0.3 mg/kg of caffeine hourly (except during naps) starting 22 hours into the 88-hour extended wakefulness period in the laboratory. The last baseline sleep (on the left) and the seven 2-hour naps occurring every 12 hours are marked with gray bars. Times of caffeine pill administration are indicated with tic marks on the top of the graph. The five 12-hour segments used for data analyses are indicated with Roman numerals on the top of the graph.

placebo conditions. Each laboratory sleep period was recorded polysomnographically (EEG C3/O2; EOG LOC/ROC; EMG; ECG) and scored using conventional criteria.²⁵ In addition, the EEG (C3) was subjected to spectral analysis to derive slow-wave energy (power in the 0.5–4.0 Hz frequency band, integrated across non-REM sleep). All subjects had relatively normal baseline sleep.

Analyses focused on the consecutive 12-hour segments of the experiment around each of the last five naps. This part of the experiment involved differential pharmacological conditions.

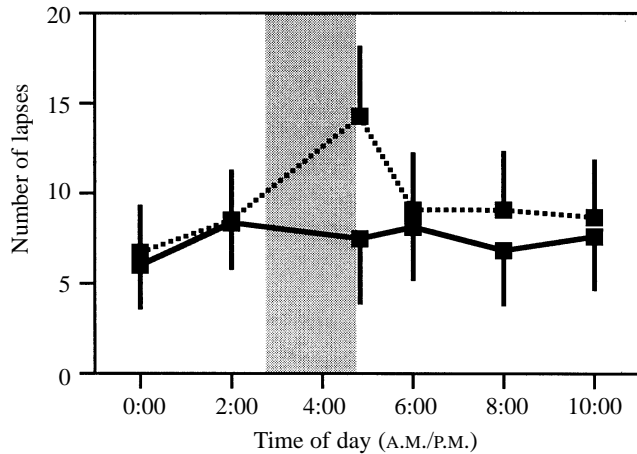


Figure 3—Psychomotor vigilance performance and sleep inertia. Mean number of performance lapses (total per test bout) and standard errors of the mean (vertical bars) on the psychomotor vigilance task are shown. Dotted lines indicate the placebo condition; solid lines indicate the caffeine condition. The data are presented as collapsed over the consecutive 12-hour segments around the last five naps of the experiment. Thus, the abscissa is collapsed over P.M. and A.M. times of day; naps (gray bar) took place from 14:45 until 16:45 and from 02:45 until 04:45. Sleep inertia was consistently observed immediately after each nap in the placebo condition, but not in the caffeine condition.

Each 12-hour segment consisted of two performance test bouts preceding a nap, and four performance test bouts following a nap. The third test bout in each segment fell immediately after the nap (i.e., during a period in which sleep inertia would be expected to be present). Analyses involved repeated-measures analysis of variance (ANOVA) with Huynh–Feldt correction, considering segment number by test bout by condition for psychomotor vigilance performance, and considering nap number by condition for nap sleep variables. Furthermore, Student's *t*-tests were applied for comparisons of means between the two conditions. All data analyses were completed blind to pharmacological condition.

RESULTS

Caffeine Concentrations

As mentioned above, analyses focused on the consecutive 12-hour segments of the experiment around each of the last five naps. During these segments, which each contained six psychomotor vigilance test bouts, significant plasma concentrations of caffeine ($t_{12} > 4.4$, $p < 0.001$) were detected in the caffeine condition, but not in the placebo condition. Caffeine concentrations in blood plasma are shown in Figure 2. When asked whether caffeine or placebo was administered in the previous hour, subjects' success in perceiving what they had received was not significantly better than chance (placebo condition: $t_{12} = -0.599$, $p = 0.56$; caffeine condition: $t_{14} = -1.480$, $p = 0.16$), and there was no difference between conditions ($t_{26} = 0.259$, $p = 0.80$).

Psychomotor Vigilance Performance

Repeated-measures analysis of variance (ANOVA) of the number of lapses on the psychomotor vigilance task yielded a significant test bout by condition interaction ($F_{5,130} = 4.901$, $p = 0.003$). Post-hoc *t*-tests showed that this was due solely to the test bouts following immediately after each nap ($t_{138} = 2.585$, $p = 0.011$). Paired-samples *t*-tests further revealed that for the placebo condition, the number of lapses during these test bouts (14.3 on average) was significantly higher than the number of lapses during the preceding (pre-nap) test bouts (8.5 on average, $t_{64} = 3.503$, $p = 0.001$) and the succeeding (post-nap) test bouts (9.1 on average, $t_{64} = 5.164$, $p < 0.001$). In contrast, for the caffeine condition, the number of lapses during the test bouts immediately following nap sleep (7.5 on average) fell slightly below the number of lapses during the preceding (pre-nap) and succeeding (post-nap) test bouts (8.4 and 8.1 on average, respectively, $p > 0.3$). Figure 3 shows the number of psychomotor vigilance lapses across test bouts, collapsed over the five 12-hour segments. Figure 4 shows these data for each separate 12-hour segment. The panels in Figure 4 might suggest differences in the magnitude of sleep inertia in the placebo condition for daytime versus nighttime naps, or for later versus earlier naps. However, the psychomotor vigilance profiles for each of the two conditions did not vary significantly across the five panels in Fig. 4 ($F_{20,520} = 0.885$, $p = 0.54$).

The difference between conditions for the test bouts immediately following nap sleep was also reflected in the results for the 10% fastest reaction times ($p < 0.001$) and the reciprocal of the 10% slowest reaction times ($p = 0.017$) on the psychomotor vigilance task. No differences in psychomotor vigilance between the two pharmacological conditions were found before pill administration began ($p > 0.6$). Also, no differences between conditions were detected during the pill administration period when test bouts immediately following the naps were excluded from the analysis ($p > 0.5$). Due to the limited time for nap sleep in the 88-hour period of extended wakefulness, however, overall psychomotor vigilance performance decreased significantly across the pill administration period in both pharmacological conditions ($F_{4,104} = 7.152$, $p = 0.002$).

Polysomnography

Repeated-measures ANOVA of polysomnographically determined sleep latency across the last five naps yielded a significant effect of pharmacological condition ($F_{4,104} = 8.838$, $p = 0.006$); sleep latency was on average 9.7 minutes longer in the caffeine condition than in the placebo condition. For total sleep time, repeated-measures ANOVA yielded significant effects of nap number ($F_{4,104} = 6.274$, $p < 0.001$) and pharmacological condition ($F_{1,26} = 9.636$, $p = 0.005$), and a significant nap number by condition interaction ($F_{4,104} = 3.516$, $p = 0.015$). Post-hoc *t*-tests revealed that the third ($t_{26} = 3.442$, $p = 0.002$) and sixth ($t_{26} = 2.165$, $p = 0.040$) nap periods only, had shorter sleep durations in the caffeine condition than the placebo condition.

For rapid eye movement (REM) sleep, a significant effect of pharmacological condition was found ($F_{1,26} = 4.531$, $p = 0.043$), with the caffeine condition resulting in an average of 5.2 minutes less REM sleep than the placebo condition. Repeated-measures ANOVA of non-REM sleep yielded a significant nap number by condition interaction ($F_{4,104} = 2.830$, $p = 0.034$). Post-hoc *t*-tests

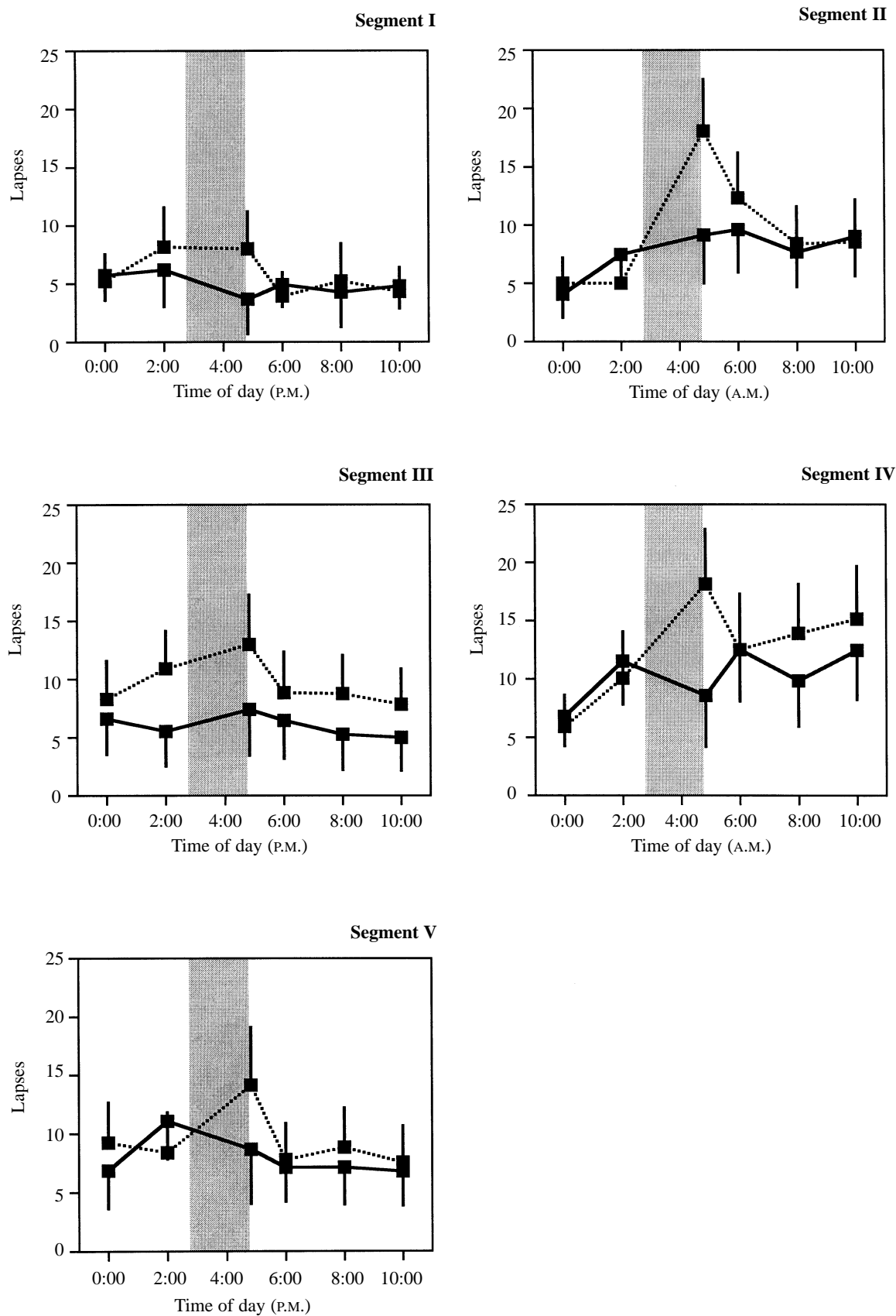


Figure 4—Psychomotor vigilance performance and sleep inertia for each of the five analyzed 12-hour segments of the experiment. Mean number of performance lapses (total per test bout) and standard errors of the mean (vertical bars) are shown. Dotted lines indicate the placebo condition; solid lines indicate the caffeine condition. Left-hand panels (segments I, III and V) correspond to daytime naps (gray bars; from 14:45 until 16:45), and right-hand panels (segments II and IV) correspond to nighttime naps (gray bars; from 02:45 until 04:45). The psychomotor vigilance profiles for each of the two conditions did not vary significantly across the five consecutive 12-hour segments.

revealed that the third nap only, had significantly less non-REM sleep in the caffeine condition than in the placebo condition ($t_{26}=3.580$, $p=0.001$). For slow-wave energy, a marker of the integrated intensity of non-REM sleep,²⁶ a trend for a nap number by condition interaction was found ($F_{4,104}=2.129$, $p=0.089$), with post-hoc t-tests indicating less slow-wave energy in the caffeine condition for the third ($t_{26}=2.502$, $p=0.019$) and fourth ($t_{26}=2.754$, $p=0.011$) naps only.

DISCUSSION

Caffeine is considered the most widely used central nervous system stimulant.¹⁹ It is readily available for oral consumption, coffee being the most common source.²⁷ Many people take caffeine in the form of a cup of coffee after awakening, at a time when the homeostatic drive for sleep would be expected to be reduced²⁶ and there would appear to be no reason to use a stimulant. However, the consumption of a caffeine-containing beverage could be effective to counter the influence of an adverse circadian phase for awakening.²⁸ This in an unlikely explanation, though, as sleep inertia occurred after nighttime as well as daytime naps in the present study, and caffeine was equally potent as a countermeasure in both instances.

As part of a large body of contradictory literature, it has been suggested that caffeine intake after awakening is related to negating withdrawal effects from the caffeine abstinence during sleep.^{19,29} The present study did not provide any support for this hypothesis. Sustained low-dose caffeine was beneficial after awakening from each of the five naps, while clearly no caffeine abstinence occurred during this period of sustained low-dose caffeine administration.

It has also been proposed that caffeine after awakening may help to suppress the build-up of homeostatic drive for sleep at a time when this build-up is believed to occur at a much faster rate than later during wakefulness.³⁰ In the present study, however, no difference between pharmacological conditions was detected in psychomotor vigilance performance when test bouts immediately following the naps (i.e., those affected by sleep inertia) were excluded from the comparison, which indicates that the build-up of homeostatic drive for sleep was the same in both conditions. The proposed effect of caffeine on the homeostatic drive for sleep³⁰ has recently been disputed by others³¹ as well. For individuals following a regular nighttime sleep schedule, the sleepiness associated with the build-up of homeostatic drive for sleep after awakening is countered by increasing circadian drive for wakefulness.^{32,33} Therefore, explaining the consumption of caffeine-containing beverages after awakening in the morning in terms of the homeostatic drive for sleep,³⁰ would require individuals to take caffeine prophylactically rather than in reaction to a need for caffeine already felt. It is unlikely that millions of individuals around the world would do this spontaneously.

Based on the present findings, we hypothesize that people take caffeine-containing beverages shortly after awakening as a countermeasure for sleep inertia, whether or not they are explicitly aware of this. A caffeine-containing beverage, such as coffee, provides a bolus of caffeine that reaches its peak blood plasma concentration within half an hour after intake on average.³⁴ It is essentially completely bioavailable, and passes the blood-brain barrier almost immediately.³⁵ This results in a similar pharmacological state as was achieved by means of sustained low-dose caf-

feine administration in our study. Thus, with a caffeine-containing beverage after awakening, sleep inertia can be reduced much more quickly than the one to two hours it may take to dissipate naturally.^{15,16} Caffeine did not appear to lose its efficacy to eliminate sleep inertia over days in the experiment. Furthermore, the elimination of sleep inertia did not appear to depend on the presence of caffeine during prior sleep (see below). Consequently, drinking a caffeine-containing beverage after awakening may be similarly efficacious for eliminating sleep inertia.³⁶ This may be the reason why many people habitually drink caffeine-containing beverages, such as coffee, after awakening.

In subjects not deprived of sleep, caffeine has been reported to interfere with the expression of non-REM sleep.³⁷ Therefore, it would be possible that sustained low-dose caffeine reduced sleep inertia in our study by diminishing prior non-REM sleep. There are several lines of evidence against this. Firstly, caffeine eliminated sleep inertia consistently in the face of increasing pressure for non-REM sleep due to the limited amount of time for sleep across the 88 hours of extended wakefulness. Secondly, we found evidence that non-REM sleep onset was delayed, but no evidence that non-REM sleep duration or intensity was consistently suppressed by caffeine across all five naps potentially affected. Thirdly, the restorative effect of the naps on overall psychomotor vigilance appeared to be equivalent in both conditions, as no difference was detected for the number of psychomotor vigilance performance lapses when test bouts immediately following the naps (i.e., during sleep inertia) were excluded from the comparison. In conclusion, caffeine's elimination of sleep inertia appeared not to be dependent on a reduction of prior non-REM sleep.

The caffeine concentrations observed in blood plasma are a good indicator of the caffeine concentrations in the brain.³⁸ Caffeine (1,3,7-trimethylxanthine) and its major metabolite³⁹ paraxanthine (1,7-dimethylxanthine) are known to antagonize adenosine receptors in the brain.⁴⁰ This is caffeine's main mechanism of action on the central nervous system⁴¹ for the caffeine concentration range used in the present study. Hypothesizing that the function of sleep is restoration of brain energy metabolism, Benington and Heller⁴² postulated that cerebral glycogen depletion during extended wakefulness induces increasing adenosine release, augmenting the drive for sleep through binding at A_1 adenosine receptors. They argued that during subsequent non-REM sleep, the resynthesis of cerebral glycogen would be possible while adenosine release continues. Upon abrupt awakening from non-REM sleep, increased levels of adenosine and the corresponding vigilance-reducing and sleep-inducing effect⁴³ could persist until adenosine is removed by reuptake or metabolism. This may cause the phenomenon of sleep inertia—a testable implication of the hypothesis of Benington and Heller.⁴²

Indeed, sleep inertia appears to intensify with prior sleep loss,^{4,5,6} and it is more severe when awakening occurs from non-REM sleep than from REM sleep.^{8,9} In the present study, which involved sleep loss (i.e., less than four hours of sleep per 24 hours), 85% of awakenings occurred out of non-REM sleep in the placebo condition, for which sleep inertia impairment in psychomotor vigilance performance was consistently seen. Sleep inertia after awakening from nap sleep was not evident in the caffeine condition. Furthermore, no difference between conditions was detected for psychomotor vigilance during test bouts not

immediately following nap sleep, indicating that caffeine's effect was specific to sleep inertia. These observations are all in line with the above implication of the hypothesis of Benington and Heller,⁴² suggesting that adenosine may be a neurobiological substrate of sleep inertia.

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