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Low-Dose Repeated Caffeine Administration for Circadian-Phase-Dependent Performance Degradation During Extended Wakefulness

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Objective: To investigate whether the effectiveness of a novel high-frequency low-dose caffeine regimen in counteracting the deterioration of performance during extended wakefulness is related to its interaction with homeostatic or circadian signals modulating performance and sleep propensity.

Design: Double-blind, placebo-controlled, parallel-group design in a 29-day forced desynchrony paradigm in which the period of the sleep-wake cycle was scheduled to be 42.85 hours, i.e., far removed from the circadian range. This design allowed for separate estimation of the sleep homeostatic, circadian, and caffeine contributions to performance deficits or improvements.

Setting: Private suite of a general clinical research center, in the absence of time of day information.

Participants: Sixteen healthy normal-sleeping men (aged 18-30 years)

Interventions: Caffeine (0.3 mg per kg per hour) or placebo was administered hourly during the 28.57-hour wake episodes.

Results: Plasma caffeine concentrations rose in an exponential saturat-

ing manner during wakefulness. Rising caffeine levels markedly attenuated wake-dependent deterioration of a number of measures of cognitive performance, particularly at the circadian performance nadir. Moreover, caffeine enhanced the ability of subjects to remain consistently awake for extended periods, holding subjects back from completing the full transition to sleep, but at the expense of increasing subjective sleepiness.

Conclusions: High-frequency low-dose caffeine administration is effective in countering the detrimental performance effects of extended wakefulness. These data are in accordance with the hypothesis that adenosine is a mediator of performance decrements associated with extended wakefulness and may lead to new strategies to use caffeine in situations in which neurobehavioral functioning is affected by sleep loss.

Key Words: sleep, circadian rhythms, caffeine, cognitive performance, alertness

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INTRODUCTION

SLEEP PROPENSITY AND WAKING PERFORMANCE ARE REGULATED BY A FINE-TUNED INTERACTION OF SLEEP HOMEOSTASIS AND CIRCADIAN RHYTHMICITY.¹⁻³ Disruption of this fine-tuned interaction, such as occurs during displacement of sleep to the daytime, leads to sleep loss and performance decrements. The profound impact of sleep loss on human performance efficiency, health, and safety is well documented, and the need to develop effective countermeasures that are based on our current understanding of the physiology of sleep and performance regulation is recognized. (reviewed in ⁴⁻⁶) Prophylactic naps^{7,8} and ingestion of prescription wake-promoting therapeutics such as modafinil⁹ have shown the ability to mitigate some of the alertness and cognitive performance deficits consequent to sleep loss. Caffeine, the most widely utilized wake-promoting substance in the world,¹⁰ has been evaluated for minimizing impairments of neurobehavioral functioning related to altered timing of sleep and wake as occurs in shift work, when driving a motor vehicle in the morning after reduced sleep time,¹¹ and with protracted sleep loss as is routinely encountered by emergency services personnel, medical house staff, and the military.^{12,13} However, many of these studies confounded the 2 major contributing processes, i.e., circadian phase and duration of prior wakefulness.^{2,3,14-16}

Adenosine has been proposed as a mediator of sleep homeostasis.¹⁷⁻¹⁹ This indicates that caffeine promotes wakefulness and performance primarily by interacting with homeostatic aspects rather than the circadian aspects of sleep propensity and performance. This would imply that the most effective way to use caffeine as a countermeasure for sleep-loss-related performance decrements would be to administer the adenosine-receptor antagonist caffeine in parallel with accumulating sleep homeostatic pressure. To test this model, we studied the efficacy of repeated low-dose caffeine administration during a forced desynchrony protocol that allowed quantification of circadian and sleep-wake dependent modulation of performance. This administration regimen contrasts with past investigations, in which caffeine was administered in a large bolus dose or doses, resulting in spike-and-fall plasma concentrations inconsistent with the hypothesized monotonic accumulation of sleep homeostatic pressure. A large bolus dose was also avoided to minimize the likelihood of dose-dependent side effects (e.g., tremor). Also, duration of scheduled wake episodes was increased nearly 10 hours over existing forced desynchrony protocols¹⁶ to further increase the acute and chronic challenge from sleep homeostatic drive.

METHODS

Participants and Screening Procedures

Potential subjects, men aged 18 to 30 years, were recruited from the Boston area by poster, radio, and newspaper advertisements. Women were not studied at the direction of the funding agency for this project. After telephone prescreening, potential subjects were given questionnaires, a history and physical examination, a psychological examination, a 12-lead electrocardiogram, and standard blood and urine screening studies. Exclusionary criteria included current medical disease or injury, evidence of sleep disorders, or personal or family history of psychopathology. Written informed consent was obtained after a long in-person discussion of all protocol elements with an investigator, accord-

Disclosure Statement

No significant financial interest/other relationship to disclose.

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ing to the standards of the Human Research Committee of the Brigham and Women's Hospital, in accordance with the Declaration of Helsinki. Subjects were asked to abstain from the intake of alcohol, caffeine, illicit substances, or medications for at least 2 weeks prior to the study, verified both during screening and upon admission via urine toxicologic analysis. Subjects kept regular sleep-wake schedules for at least 3 weeks, verified during the final week via wrist actigraphic monitoring. Subjects were required to attempt to sleep for 8 hours, with bedtimes and wake times varying by no more than ± 30 minutes from self-selected times.

Imposed Wake-Sleep and Light-Dark Schedule

We studied 16 healthy normal-sleeping men in a 29-day inpatient protocol (protocol illustrated in Figure 1). Admission was to a private suite, free of obvious time cues. Lighting was provided via ceiling-mounted fluorescent fixtures, < 15 lux during scheduled wake episodes and approximately 0.03 lux during scheduled sleep episodes, conditions designed to induce minimal relative coordination of the circadian pacemaker from the light-dark cycle.²⁰ Following 3 repetitions of a baseline 24-hour cycle (16-hour wake episodes and 8-hour sleep episodes), subjects were scheduled on a forced desynchrony protocol with 14 repetitions of a noncircadian 42.85-hour activity-rest and light-dark cycle (28.57-hour wake episodes and 14.28-hour sleep episodes) occurring over twenty-five 24-hour days. Subjects were required to remain awake during scheduled wake episodes and to remain lying down in bed during scheduled sleep episodes. The 42.85-hour cycle was selected to allow for wake and sleep episodes to be distributed across a range of circadian phases throughout the inpatient stay and to have relatively long wake episodes, similar in duration to extended duty hours commonly encountered by emergency services personnel, medical house staff, and military personnel.

Caffeine and Placebo Administration

During the 3 baseline wake episodes, all subjects ingested 1 placebo capsule per hour, under single-blind conditions. Hourly during forced-desynchrony wake episodes, now under double-blind conditions and in a between-groups design, subjects ingested either caffeine capsules ($n = 8$, 0.3 mg per kg per hour) or identical-appearing placebo ($n = 8$), beginning 1 minute after wake time and terminating 1.57 hours prior to bedtime. After conducting extensive mathematical modeling of various dose and timing options assuming peak absorption at approximately 45 minutes and half life of 3 to 7 hours,²¹ a dose of 0.3 mg per kg per hour and hourly administration were selected to produce caffeine concentrations well within the range found during normal consumption, while likely avoiding significant side effects or binding to other receptor systems aside from adenosine. Electroencephalogram (EEG) power spectra and plasma melatonin data from the placebo subjects have been reported elsewhere.²²

Physiologic Monitoring and Neurobehavioral Assessment

Polysomnographic monitoring was conducted for each sleep episode, with scalp EEG, electrooculogram, chin electromyogram, and 2-lead electrocardiogram. Thirty-second epochs were scored according to standard criteria,²³ with scorers blinded to drug condition.

During scheduled wake episodes, mood and subjective sleepiness were assessed each 30 minutes with visual analog scales (SCALES) and the Karolinska Sleepiness Scale (KSS). Cognitive performance was assessed each 2 hours with a 30-minute test battery consisting of the Probed Recall Memory Task (PRM – short-term memory), the Psychomotor Vigilance Task (PVT – visual vigilance and simple reaction time), the Addition Task (ADD – cognitive throughput), the Digit Symbol Substitution Task (DSST – cognitive throughput) (tasks reviewed in Wyatt et al.³). The EEG and electrooculogram were recorded throughout the majority of each scheduled wake episode, beginning approximately 3 hours after scheduled wake time. Incidences of slow eye movements and unintentional sleep onsets were quantified as 2

physiologic measures of impairment in neurobehavioral functioning.¹⁵ Technicians also verbally awakened subjects, by calling their names, after detecting unintentional sleep onsets from the EEG recordings. During their free time, subjects were allowed to read, study, write letters, watch prerecorded movies or television programs, listen to taped music, or chat with the staff technicians and nurses.

Core body temperature was recorded each minute via rectal temperature sensor. From Day 2 of the protocol through discharge, hourly blood samples were obtained via a forearm intravenous catheter. Plasma was separated via centrifugation under 2°C at 2200 to 2800 revolutions per minute, frozen at -25°C, and shipped for assay of caffeine (Pennington Biomedical Research Center, Baton Rouge, LA; assay sensitivity 0.1-0.3 μg per milliliter) and endogenous melatonin (DiagnosTech, Osceola, WI, USA; assay sensitivity 10.1 pmol per liter). Each subject's intrinsic circadian period was estimated by nonorthogonal spectral analysis²⁴ of every sixth minute of the core body temperature and every hour of melatonin data collected during forced desynchrony. In addition to providing estimations of intrinsic period, the analyses yielded an estimate of the first core body temperature minimum and the first plasma melatonin maximum during forced desynchrony. This allowed separation of evoked effects from the 42.85-hour rest-activity cycle from the near 24-hour intrinsic oscillation of core body temperature and melatonin.

Assignment of Level for Circadian Phase and Sleep Homeostatic Drive

The dependent variables (sleep, waking electrophysiologic data, and neurobehavioral assessments) were assigned a circadian-phase bin based on the period and phase data from the melatonin samples. Dependent variables were also binned by either duration of prior scheduled wakefulness (neurobehavioral assessments, waking electrophysiologic data) or prior scheduled sleep (sleep data). For each neurobehavioral measure, a 3-way, repeated-measures analysis of variance was conducted, with the factors of drug condition (DRUG), circadian phase (PHASE), and duration of prior scheduled wakefulness (WAKE). One subject was omitted

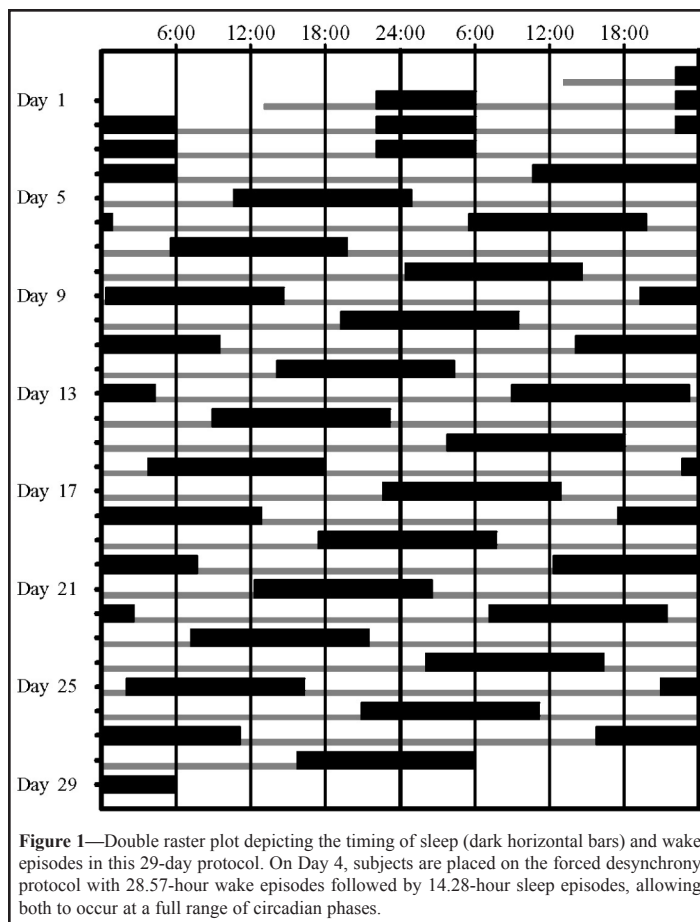


Figure 1—Double raster plot depicting the timing of sleep (dark horizontal bars) and wake episodes in this 29-day protocol. On Day 4, subjects are placed on the forced desynchrony protocol with 28.57-hour wake episodes followed by 14.28-hour sleep episodes, allowing both to occur at a full range of circadian phases.

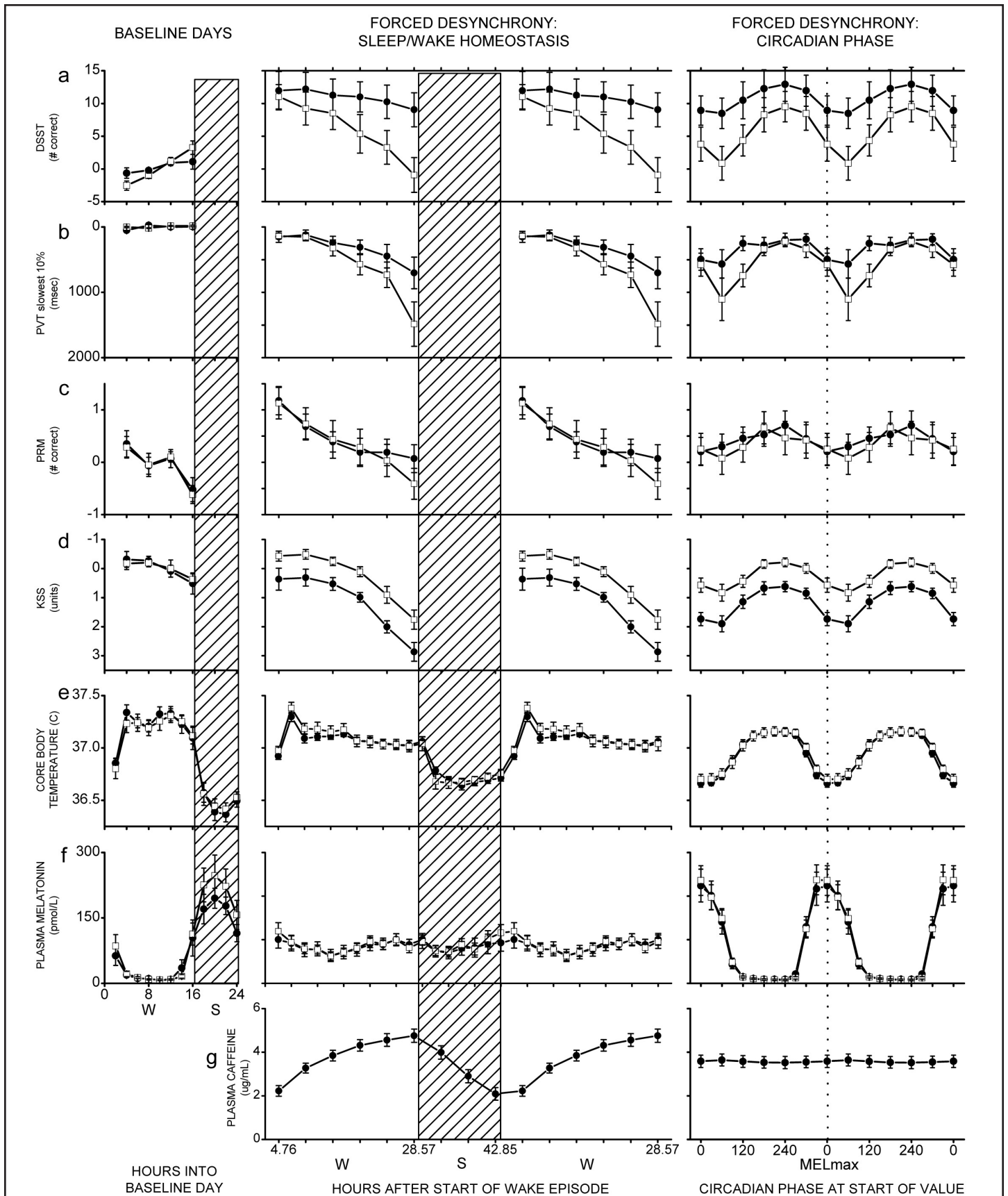


Figure 2—Neurobehavioral functions by sleep homeostasis and circadian phase. Modulation of selected cognitive performance (panels a, b, c), subjective alertness (panel d), and physiologic data (panels e, f, g) from the 16-hour wake episodes of the baseline protocol segment (left column), averaged across the 14 forced desynchrony cycles and double plotted as a function of duration of prior wakefulness or sleep with 28.57-hour wake episodes and 14.28-hour sleep episodes (middle column), and as a function of double-plotted circadian phase relative to the melatonin maximum (right column). For all plots, subjects in the caffeine condition are displayed with filled circles (●) and subjects receiving placebo with open squares (□). Dimensions of the x-axes are equated for equal units of clock time. Units of the y-axes are identical for each measure for the left, middle, and center panels. The data represent mean values (\pm SEM), averaged first within subject and then across subjects within drug condition. For cognitive performance and subjective alertness plots, a value of 0 represents the mean value for each subject during the baseline (left column) protocol segment. DSST refers to the number correct on Digit Symbol Substitution Task; PVT, the slowest 10% of reaction times on the Psychomotor Vigilance Task; PRM, the number correct on the Probed Recall Memory task; KSS, the rating on the Karolinska Sleepiness Scale; MELmax, maximum of the plasma melatonin level.

from the DSST analysis due to missing baseline data. Five subjects were omitted from the analyses of waking slow eye movement and accidental sleep onset due to missing data.

RESULTS

Circadian Period

As expected, subjects' circadian pacemakers were unable to synchronize to the imposed 42.85-hour cycle. Mean (\pm SD) estimates of intrinsic circadian period derived from core body temperature data were 24.33 hours (\pm 0.27) for the caffeine group and 24.20 hours (\pm 0.14) for the placebo group (2-tailed, Student *t* test, NS), and mean estimates of intrinsic circadian period derived from melatonin data were 24.34 hours (\pm 0.28) for the caffeine group and 24.21 hours (\pm 0.13) for the placebo group (2-tailed, Student *t* test, NS).

Plasma Caffeine Concentration

Caffeine plasma concentration rose throughout the wake episodes in a progressive exponential saturating manner. Plasma caffeine levels did not completely clear prior to starting each new wake episode. No significant circadian modulation of plasma caffeine concentration was detected (Figure 2g).

Caffeine Effect on Physiologic Sleepiness, Sleep, and Subjective Alertness

When sleep episodes were scheduled just prior to the onset of melatonin secretion, subjects in the caffeine condition experienced lower sleep efficiency (DRUG \times PHASE interaction, $P < .02$; Figure 3a). During scheduled wake episodes, subjects in the caffeine group showed an impressive attenuation of the wake- and circadian-dependent modulation of unintentional sleep onsets, with main effects of DRUG condition and interactions between DRUG and WAKE and DRUG and PHASE (Table and Figure 3b). In the placebo condition, there was a high incidence of unintentional (accidental) sleep onsets at the end of the wake episodes, at the circadian phase just following the trough of core body temperature and the peak of melatonin. Based on EEG verification, subjects receiving placebo were unintentionally asleep 1.57% of the time during the scheduled wake episodes, versus only 0.32% for the subjects receiving caffeine ($p = 0.005$). Incidence of slow eye movements during wake episodes, a second marker of physiological sleepiness, did not differ significantly between drug conditions (b and c in Figure 3 and Table).

Additional sleep accumulated by the placebo subjects during scheduled wake and sleep episodes was associated with reduced self-report of sleepiness independent of circadian phase or duration of prior scheduled wakefulness. Subjects in the caffeine group self-reported more impairment of alertness on both the KSS and SCALES measures (main effects of DRUG, both $P < .05$; Figure 2d). However, there was a distinct difference in the pattern of subjective sleepiness reported between the first

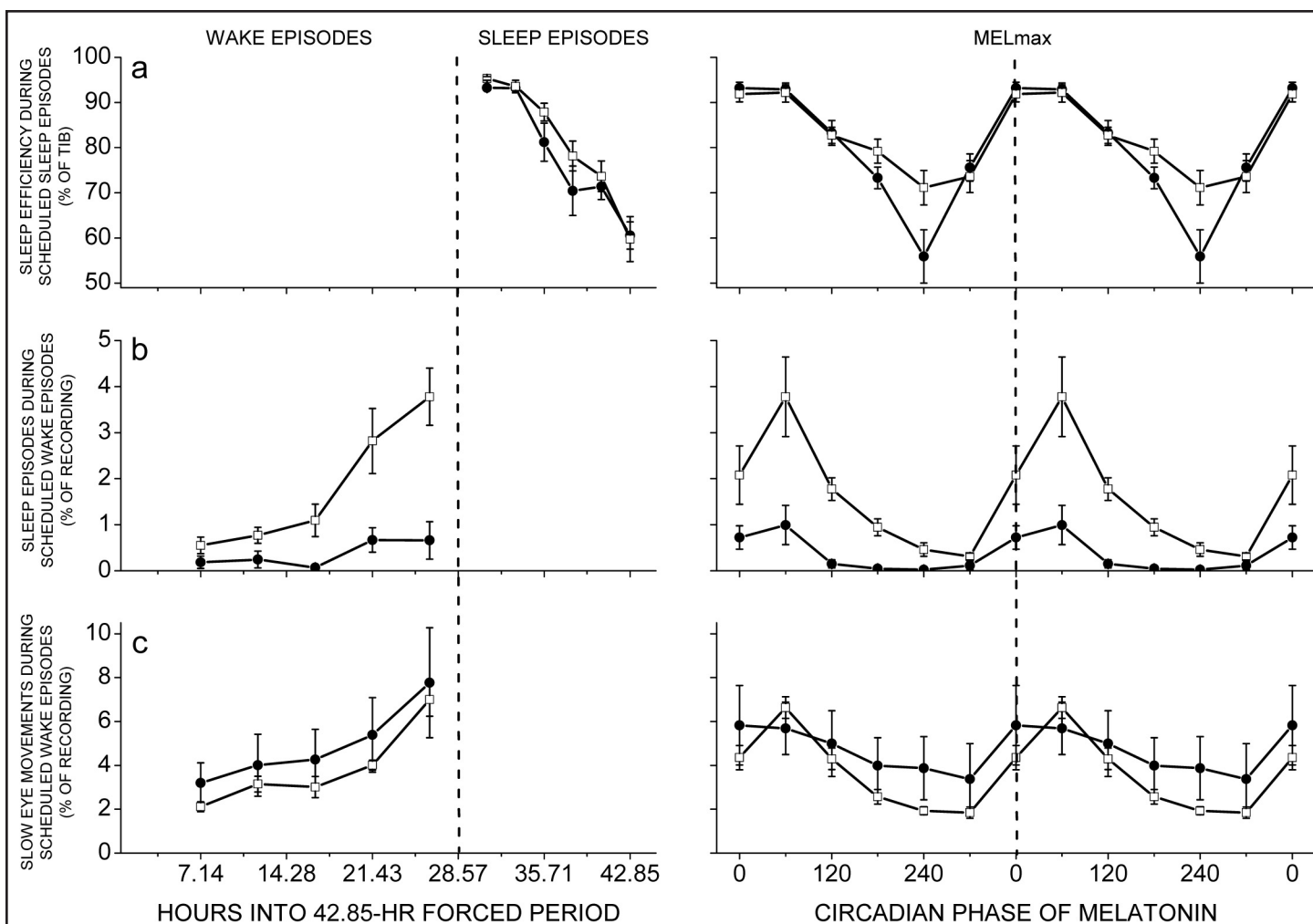


Figure 3—Modulation of sleep consolidation during (a) scheduled sleep episodes, (b) unintentional sleep onsets and (c) slow eye movements recorded during the 28.57-hour wake episodes, by sleep homeostasis (left panels) or circadian phase (right panels). For sleep consolidation, sleep efficiency was calculated as the percentage of all epochs scored as sleep divided by the total number of epochs, within each sleep episode bin (a, left) or circadian-phase bin with 0 degrees corresponding to the peak of plasma melatonin (a, right). Dimensions of the x-axes are equated for equal units of clock time. The caffeine group is shown with filled circles (●) and the placebo group with open squares (□). The data represent mean values (\pm SEM), averaged first within subject and then across subjects within drug condition. TIB refers to time in bed; MELmax, maximum of the plasma melatonin level.

and all subsequent 28.57-hour wake episodes (Figure 4). Subjective sleepiness during the baseline wake episodes was equivalent across groups. On the first long wake episode, acute exposure to caffeine was associated with an attenuation of the buildup of subjective sleepiness seen in the placebo group. After the sleep episode following this first administration of caffeine, this effect was reversed.

Caffeine Effect on Cognitive Performance

Caffeine attenuated the wake-dependent impairment for the number of correct responses on the 2 cognitive throughput tasks, ADD and DSST, ($P < .05$; Figure 2a demonstrates effect for DSST). The caffeine group also showed less evidence of wake-dependent impairment on the PVT, as indicated by both the total number of lapses (reaction times longer than 500 milliseconds) and the slowest 10% of reaction times (both $P < .05$; Figure 2b). There was also a statistical trend for less wake-

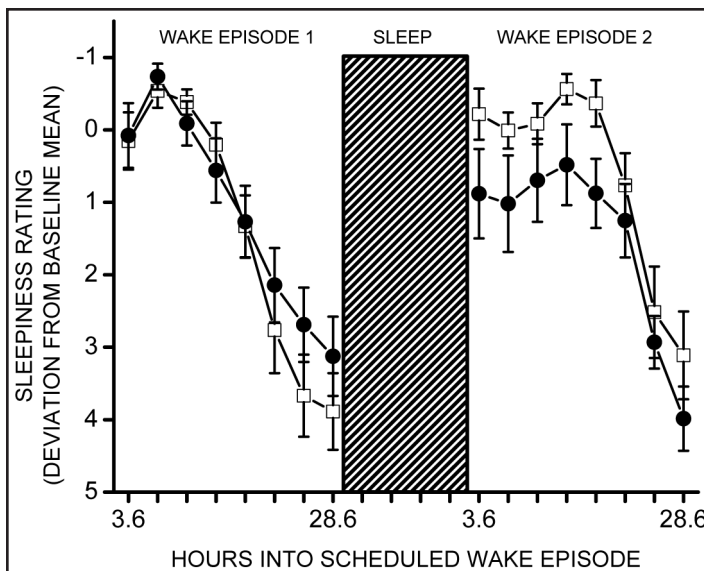


Figure 4—Modulation of subjective sleepiness for the first (left panel) and second (right panel) 28.57-hour scheduled wake episodes. For this analysis, Karolinska Sleepiness Scale mean values (\pm SEM) for subjects in the caffeine condition are displayed with filled circles (\bullet) and subjects receiving placebo with open squares (\square). A value of 0 represents the mean value for each subject during the baseline protocol segment with 16-hour wake episodes.

dependent impairment of short-term memory on the PRM task for the caffeine group but with differences emerging only toward the end of the extended wake episodes ($P < .09$; Figure 2c). Caffeine reduced the circadian phase-dependent decrement in total number of correct responses on the DSST (DRUG \times PHASE, $P < .01$), and there was a trend for a similar dampening of circadian modulation on the number of ADD correct responses and PVT lapses. This appears to be related to attenuating the degree of impairment near the circadian trough (Figure 2a and 2b, right panels).

Circadian and Sleep-Wake-Dependent Modulation of Neurobehavioral Functions and Sleep

There was wake-dependent and circadian modulation of subjective alertness ratings from both the KSS and the SCALES (Table; main effects of WAKE and PHASE from combined data from both the placebo and caffeine conditions; all P values $< .0001$). Subjects self-reported greatest impairment of alertness late in the wake episodes and at the circadian phase normally encountered near wake time. There were interactions of WAKE and PHASE for both alertness measures, with amplitude of circadian modulation increasing as a function of increasing duration of prior wakefulness (both P values $< .002$; Figure 5d). Drug condition did not interact with either WAKE or PHASE, showing that the greater impairment in alertness for the caffeine group was independent of duration of prior wakefulness or circadian phase. Cognitive performance on nearly all tasks showed main effects for WAKE and PHASE (all P values $< .05$). Specifically, performance was most impaired toward the end of the 28.57-hour wake episodes and at the circadian alertness nadir normally encountered near habitual wake time (Figure 2a, b, and c). Also, for most measures, there were interactions of WAKE and PHASE; amplitude of circadian modulation in performance was minimal at the beginning of the wake episodes, growing larger throughout the duration of scheduled wakefulness (all P values $< .05$). This is illustrated in the contour plots (Figure 5a, b, and c). Finally, a strong circadian modulation of sleep consolidation was noted (analysis of variance; $F = 39.16$, $P < .0001$), with maximal sleep efficiency observed near the maximum of melatonin secretion.

DISCUSSION

There have recently been important advances in understanding the neurochemistry of sleep-wake modulation (reviewed by Mignot et al²⁵),

Table—Neurobehavioral Measures

TASK	DRUG	WAKE	DRUG \times WAKE	PHASE	DRUG \times PHASE	WAKE \times PHASE	3-WAY
COGNITIVE THROUGHPUT TASKS							
ADDITION, no. correct	3.88 (.07)	18.81 (< .0001)	4.59 (.01)	28.18 (< .0001)	2.29 (.10)	3.38 (< .0001)	1.06 (.40)
DSST, no. correct	1.90 (.19)	3.36 (< .0001)	1.89 (< .0001)	39.10 (< .0001)	4.12 (.01)	3.01 (.001)	.48 (.92)
SHORT-TERM MEMORY							
PRM, no. correct	.05 (.83)	4.55 (< .0001)	2.30 (.08)	6.13 (< .0001)	1.40 (.24)	1.18 (.27)	.91 (.58)
PSYCHOMOTOR VIGILANCE & SIMPLE REACTION TIME							
PVT, median RT	.05 (.83)	1.26 (.002)	1.12 (.33)	4.41 (.04)	1.02 (.35)	1.29 (.29)	.87 (.42)
PVT, slowest 10% RT	1.68 (.22)	2.76 (< .0001)	3.89 (.04)	8.29 (.001)	1.91 (.16)	2.80 (.02)	1.09 (.38)
PVT, no. lapses	.18 (.68)	41.89 (< .0001)	3.37 (.03)	16.80 (< .0001)	2.36 (.08)	3.16 (< .0001)	.73 (.75)
SUBJECTIVE ALERTNESS MEASURES							
KSS	12.96 (.003)	49.53 (< .0001)	.38 (.67)	24.48 (< .0001)	.80 (.54)	2.77 (.002)	1.01 (.44)
VAS	5.37 (.04)	38.16 (< .0001)	.13 (.86)	19.12 (< .0001)	.77 (.52)	2.83 (< .0001)	.96 (.52)
SLOW EYE MOVEMENTS DURING SCHEDULED WAKE EPISODES							
% of baseline	.6 (.47)	23.33 (< .0001)	.35 (.70)	17.5 (< .0001)	2.3 (.07)	2.5 (.03)	.9 (.47)
UNINTENTIONAL SLEEP ONSET DURING SCHEDULED WAKE EPISODES							
% of baseline	13.5 (.005)	11.6 (< .0001)	6.1 (.004)	14.5 (.0002)	34.6 (.03)	1.1 (.29)	1.5 (.17)

Results [F (P value)] of separate, repeated-measures analyses of variance (rANOVA) for waking neurobehavioral measures. Main effects were DRUG (caffeine or placebo), WAKE (duration of prior scheduled wake), and PHASE (circadian phase from plasma melatonin). Two-way and 3-way interactions were allowed. Significant effects are highlighted with bold text. DSST refers to the number correct on Digit Symbol Substitution Task; PVT, the slowest 10% of reaction times on the Psychomotor Vigilance Task; PRM, the number correct on the Probed Recall Memory task; KSS, the rating on the Karolinska Sleepiness Scale; VAS, visual analog scale; RT, reaction time; VAS, visual analog scale

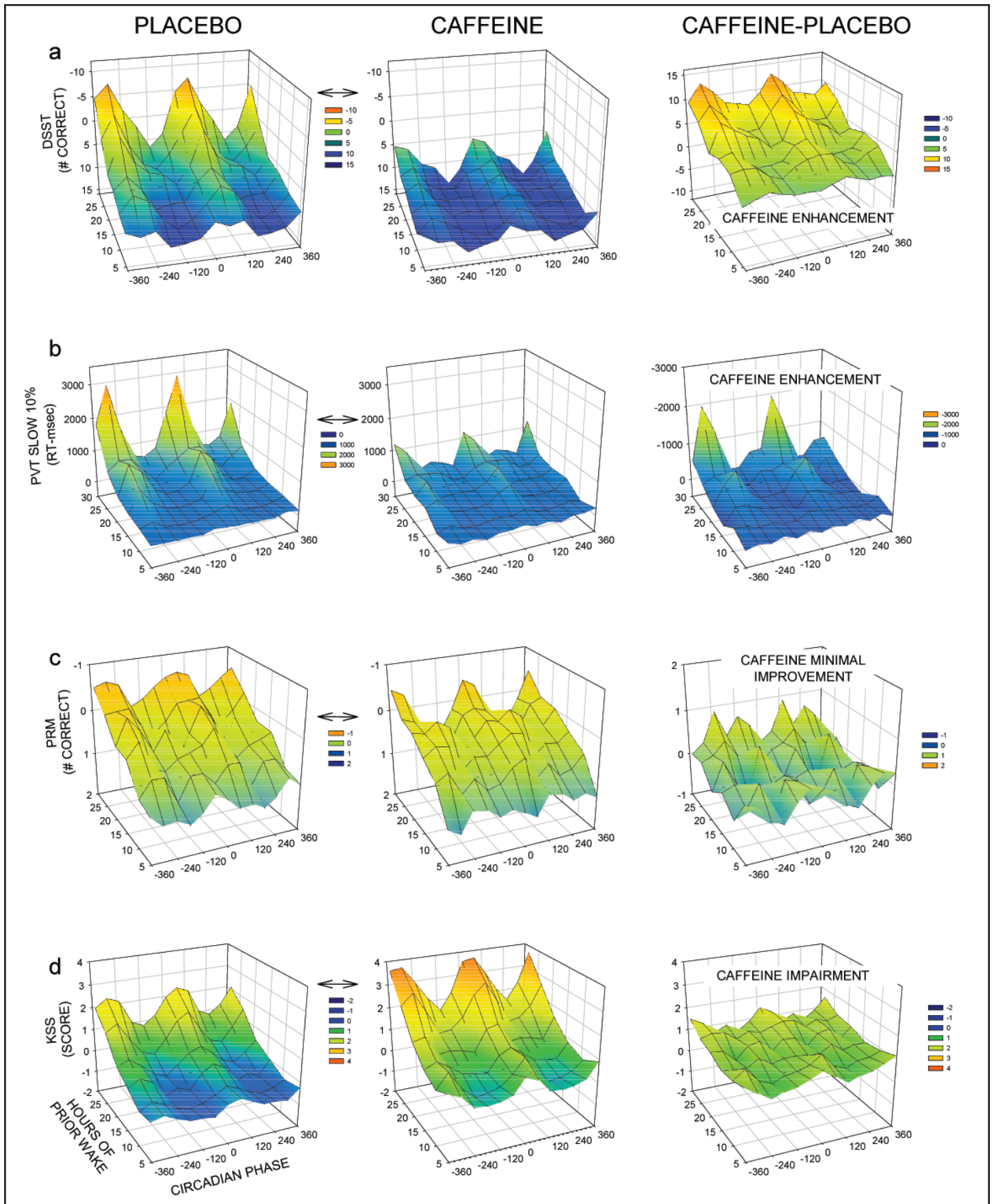


Figure 5—Interaction between the duration of prior scheduled wakefulness (y-axis of each panel) and circadian phase as measured by plasma melatonin levels (x-axis of each panel, double-plotted to highlight the transition point near the melatonin maximum, shown as 0 degrees, which corresponds to approximately 4:00 am under entrained conditions), in the modulation of selected neurobehavioral measures (z-axis of each panel, with 0 corresponding to each subject's average value from the baseline, adaptation protocol segment). The columns indicate the subjects receiving placebo only (left column), caffeine (middle column), and the difference between the 2 conditions (right column). For the left and center columns, higher values on the z-axis indicate higher levels of impairment. For the right column (except for KSS), higher values represent attenuation of deficit in the caffeine condition. DSSST refers to the number correct on Digit Symbol Substitution Task; PVT, the slowest 10% of reaction times on the Psychomotor Vigilance Task; PRM, the number correct on the Probed Recall Memory task; KSS, the rating on the Karolinska Sleepiness Scale.

the inability of the brain to compensate for chronic partial sleep loss,²⁶ and the linkages between brain structures and functioning under conditions of short-term sleep deprivation.²⁷ Use of the forced desynchrony protocol allowed us to quantify the independent contributions of and interaction between the sleep-homeostatic and circadian-timing systems in their modulation of sleep consolidation and waking functioning. The 42.85-hour cycle also allowed for simulation of extended wakefulness commonly encountered by medical and military personnel or anyone simply skipping a night of sleep.

We delivered caffeine according to a schedule designed to increase plasma concentration in parallel to the hypothesized and subsequently confirmed rate of increase in sleep homeostatic drive during wakefulness,^{14,28} itself thought to follow the accumulation of adenosine,¹⁷⁻¹⁹ receptors for which caffeine antagonizes. Average caffeine concentrations were within the range observed after typical caffeine consumption.²⁹ The significant reduction of deficits seen on several measures of neurobehavioral functioning in the caffeine condition appeared to be primarily explained through robust attenuation of wake-dependent impairment. Repeated low-dose caffeine administration was effective in offsetting deficits in 2 cognitive throughput tasks and the PVT. We also observed inhibition of EEG-verified accidental sleep onsets during scheduled wake episodes. This decrease in accidental sleep onsets—relative to the placebo group—but no difference in the number of slow eye movements between the caffeine and placebo groups, suggests that subjects receiving caffeine were kept at an earlier less-severe stage of the sleep-onset continuum,³⁰ largely prevented from progressing to full sleep onset. Subjects receiving caffeine showed impairment of polysomnographically verified sleep compared to the placebo subjects, but this difference was notable only in portions of sleep episodes occurring when the circadian timing system maximally promotes wakefulness—and at a time at which people seldom select to initiate sleep.³¹ The accumulation of additional sleep by the placebo subjects during scheduled sleep and wake, in association with lower subjective sleepiness, suggests the wake-promoting effects of caffeine do not replace the restorative effects gained through sleep. A similar paradoxical finding of increased subjective sleepiness in subjects receiving caffeine over repeated days has been reported.³²

The observed reduction in accidental sleep onsets supports the conclusion that caffeine attenuates expression of homeostatic sleep drive. Because our plasma caffeine concentrations would be expected to affect only adenosine receptors and not other mechanisms such as GABA_A receptors, breakdown of cyclic AMP, or changes in intracellular calcium,³³ and because caffeine primarily affects the sleep-wake-dependent modulation of performance, the present data are in accordance with the proposed role for adenosine in mediating sleep-wake-dependent modulation of sleep propensity and associated variation in neurobehavioral functioning. However, it is possible that substances other than adenosine may be involved in the mediation of the observed caffeine effects. Though understanding of the mechanism of action requires further clarification, systematic caffeine administration holds great promise as a countermeasure to cognitive deficits and unintended sleep attacks, at the cost of increasing subjective sleepiness. Whether the latter was due to an undetected effect of caffeine that interfered with the restorative function of subsequent sleep cannot be determined from the present study. Our data indicate that the effect of caffeine on reducing deficits in cognitive performance is predominantly through interference with the sleep-dependent (i.e., homeostatic) facet of the regulation of performance.

In general, neurobehavioral impairment was observed with increased duration of scheduled wakefulness and particularly at the “circadian sleep maintenance zone,” a term introduced here denoting the range of maximum active circadian sleep promotion normally encountered at the end of the habitual sleep episode. Also, when the subject was sufficiently challenged by extended wakefulness and adverse circadian phase, even accuracy of performance, traditionally thought to be relatively invariant,³⁴ began to show impairment. Sleep was most fragmented toward the end of the sleep episodes and at the circadian phase normally encountered at or just prior to habitual bedtime. This phase has been

termed the “wake maintenance zone,”³¹ the time of the circadian system’s maximal promotion of wakefulness. Taken together, these results from the placebo condition support the pivotal roles of sleep homeostasis and circadian phase in the modulation of sleep and waking neurobehavioral functioning. These findings also stress the importance of accounting for variance explained by sleep homeostatic and circadian modulation when interpreting data from protocols in which tests are given in only a single administration, such as typically occurs in traditional clinical and cognitive neuroscience research.

These data also reinforce previous findings^{3,15,16} that sleep homeostasis has, in addition to independent modulation, a strong effect on the amplitude of expression of the circadian rhythm of neurobehavioral functioning. With low sleep homeostatic pressure, such as would be encountered shortly after awakening from the major daily sleep episode, circadian modulation of cognitive performance and subjective alertness was minimal (or undetectable). With increasing homeostatic drive, the amplitude of the circadian modulation became equally important and reached that of the homeostatic process. Such interaction is at variance with models of neurobehavioral function with additive homeostatic and circadian components. Using these results for scheduling wake episodes to maximize task performance and minimize zones of vulnerability to performance decrements and errors, it becomes critically important to consider the interaction of sleep homeostatic drive and circadian phase.

Utilization of this novel procedure for caffeine use as a countermeasure against sleep- and circadian-related performance impairment may be of particular benefit when safety of the public is critically dependent on optimal alertness, such as in medical and surgical residents.³⁵⁻³⁷ Actually falling asleep while driving in the past year was reported by 20% of 18- to 54-year-old respondents in a recent survey in the United States,³⁸ suggesting that the general public may also benefit from an increased use of repeated low-dose caffeine to oppose the increasing homeostatic sleep drive. We would recommend studies in those target populations (e.g., hospital residents, truck drivers), comparing this caffeine administration procedure to other countermeasures, such as prophylactic napping and extension of recovery sleep. In addition to measuring simple cognitive processes as in the present study, such studies should include more complex, executive function tasks to explore potential benefit from the use of caffeine. Future research of similar duration (e.g., 1 month) could also provide data on the possible development of tolerance to caffeine over repeated administration. Tolerance could not be separated in the results from the present study due to potential confounding variables, including repeated circadian-phase misalignment and changes in effort over time related to the high frequency of test administration.

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