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The Cumulative Neurobehavioral and Physiological Effects of Chronic Caffeine Intake: Individual Differences and Implications for the Use of Caffeinated Energy Products

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Abstract

The use of caffeine-containing energy products (CCEP) has increased worldwide in recent years and research shows that CCEP can improve cognitive and physical performance. All of the top-selling energy drinks contain caffeine, which is likely to be the primary psychoactive ingredient in CCEP. Presumably, individuals consume CCEP to counteract feelings of 'low-energy' in situations causing tiredness, fatigue, and/or reduced alertness. This review discusses the scientific evidence for sleep loss, circadian phase, sleep inertia and the time-on-task effect as causes of 'low energy' and summarizes research assessing the efficacy of caffeine to counteract decreased alertness and increased fatigue in such situations. The results of a placebo-controlled experiment on healthy adults undergoing three nights of total sleep deprivation (with or without 2 hour naps every 12 hours) are presented to illustrate the physiological and neurobehavioral effects of sustained low-dose caffeine. Individual differences, including genetic factors, in the response to caffeine and to sleep loss are discussed. We conclude with future directions for research on this important and evolving topic.

The use of caffeine-containing energy products (CCEP) including caffeine-containing energy drinks (CCED) has increased worldwide in recent years. According to Symphony IRI data compiled by Bloomberg, US CCED sales increased 6.7% to $9.7 billion from 2011-2012 to 2012-2013. In one study of college students, 51% of respondents consumed at least one CCED per month[1] and data obtained from active service members showed that 44.8% consumed at least one CCED daily.[2] Although the U.S. Food and Drug Administration (FDA) does not define the term 'energy drink', products popularly

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designated, advertised or consumed as energy drinks contain stimulants and are marketed to provide the consumer with behavioral ‘energy’, improved alertness, and improved cognitive and/or physical ability.[3] Although these purported effects can encompass different neurobehavioral domains,[4] recent research has shown that the ingestion of CCEP can improve attention, reaction speed, information processing, memory, mood and aerobic performance.[5-14]

All of the top-selling energy drinks contain caffeine (approximately 30-50 mg per 100 ml, with a typical serving size being 240 ml).[3,15] In this review we focus on caffeine, as there is evidence that caffeine is the active ingredient responsible for the cognitive and physical effects of CCEP.[3,16-18] Other articles in this issue review the potential contribution of other ingredients to the effects of CCEP. Caffeine is a methylxanthine naturally found in the seeds and leaves of certain plants, which acts as a central nervous system stimulant in humans.[19] Following ingestion, caffeine is rapidly absorbed from the gastrointestinal tract into the bloodstream and passes all biological membranes, including the blood-brain barrier.[20] Caffeine exerts its effects by antagonizing adenosine (primarily A_1 and A_{2a}) receptors which are widely expressed throughout the body (including in the cardiovascular, respiratory, renal and gastrointestinal systems)[21] and in the brain (including areas believed to be involved in the regulation of sleep-wake).[22,23] Adenosine inhibits the release of various neurotransmitters (i.e., acetylcholine, noradrenaline, and dopamine); therefore, caffeine increases the release of these neurotransmitters by inhibiting adenosine.[19,24] This leads to peripheral vasoconstriction, increased blood pressure, and thermogenesis, as well as greater renal excretion of sodium and water and gastric secretion of acid and pepsin.[24,25]

Presumably, individuals consume energy products to counteract feelings of ‘low-energy’ in situations causing decreased alertness and increased fatigue. This review discusses the scientific evidence for sleep loss, circadian phase, sleep inertia and the time-on-task effect as causes of ‘low-energy’ and summarizes research assessing the efficacy of caffeine to counteract decreased alertness and increased fatigue in such situations. Individual differences in the vulnerability to sleep loss and to caffeine, including genetic factors, are also presented. We conclude with future directions for research on this important and evolving topic.

Causes of Low Energy

In healthy humans, alertness is primarily regulated by two processes: homeostatic regulation and circadian timing.[26] The homeostatic sleep-dependent process has two components, the first (process S) balances sleep propensity by tracking recent sleep history.[27] As hours of wakefulness increase, homeostatic drive increases the propensity for sleep. The second component of the homeostatic process (process U) monitors sleep-wake on a longer time scale; process U builds up over several days of prolonged wakefulness (when sleep debt is accruing).[28] The status of process U codetermines the rate by which process S increases sleep propensity and decreases alertness.[28] The endogenous circadian process (process C) tracks changes in light exposure (as well as other zeitgebers or ‘time-givers’) and entrains sleep propensity to the light-dark cycle. When sleep propensity is increased (during the night) waking performance is degraded.[29]

Sleep Loss

For most healthy adults, physiological sleep duration ranges between 7.0 and 8.5 hours; however, habitual sleep duration in adults is determined by a variety of factors and shows considerable variance within and between individuals.[30] Data from a national survey revealed that approximately 28.3% of adults in the U.S. report sleeping less than 7 hours per night[31] and two epidemiological studies found that the prevalence of being a self-reported 'short sleeper' (≤6 hours/day) has increased significantly in recent decades.[32,33] Compensated work time and travel time (which includes commuting to work) are the primary determinants of sleep duration[34] with longer work hours associated with shorter sleep duration.[35-37] Studies suggest that habitual short sleepers do not require less sleep than other adults; rather, these individuals gradually accrue sleep debt over time.[38-40] Laboratory studies examining the effects of chronic sleep restriction showed that individuals sleeping less than 7 hours per night for consecutive nights exhibited increased sleep propensity[41-45] and decreased alertness[42-48] with performance becoming progressively worse as sleep debt accumulated across days.

In addition to chronic sleep restriction, some individuals undergo prolonged periods of wakefulness without sleep ('pulling all-nighters'; acute total sleep deprivation) in order to meet deadlines for school or as part of work duties. Although population-based prevalence rates for this type of sleep loss are unavailable, certain individuals, including college students,[49] medical residents,[50] military personnel, truck drivers[51] and shift workers[52] experience total sleep deprivation routinely. Acute total sleep deprivation also increased sleep propensity and decreased alertness in laboratory studies.[46,53-55]

The increased propensity for sleep and decreased alertness due to sleep loss from chronic sleep restriction or acute total sleep deprivation can lead to 'microsleeps' (very brief sleep episodes that intrude into wakefulness despite an individual's best effort to stay awake),[56,57] and to wake-state instability. Wake-state instability refers to moment-to-moment shifts in the neurobiological systems mediating the motivated desire to sustain waking alertness and those mediating the involuntary homeostatic drive to fall asleep.[55,58] This interaction between wake and sleep drives results in unpredictable behavior, including increased variability in cognitive performance on tests requiring vigilant attention such as the Psychomotor Vigilance Test (PVT): sleep deprivation results in periods of accurate responding interrupted by errors of omission (i.e., lapses of attention that manifest as long response times) comingled with errors of commission (i.e., premature responses reflecting compensatory effort).[55,59] Although individuals may not realize they are experiencing 'microsleeps' and performance decrements, over time such behavioral instability can progress into sleep attacks (involuntary sleep bouts lasting 30 seconds or more, from which individuals cannot spontaneously awaken from without additional stimulation).[59-62]

Circadian Phase

A circadian rhythm is an endogenous 24-hour oscillatory variation in physiology and behavior. Environmental light is transmitted from the retina to suprachiasmatic nuclei (SCN, known as the central pacemaker) in the anterior hypothalamus and then to the pineal gland via a multisynaptic pathway; the pineal gland secretes melatonin, a hormone that regulates

various biological functions, including sleep-wake cycles.[63-67] In humans, melatonin levels peak during the dark cycle (which normally coincides with a period of inactivity and sleepiness) and decrease during the light cycle (which normally coincides with a period of activity and wakefulness).[68,69] Thus, the alternation of light and darkness directly entrains an organism's circadian rhythms. At night, when melatonin levels are high, sleep propensity is increased and alertness is degraded.[70] Sleep propensity/decreased alertness peaks during the early hours of the morning (02:00h-07:00h) and peaks (to a lesser degree) again in the mid-afternoon (13:00h-16:00h, known as the 'post-lunch dip').[59,71,72] Conversely, sleep propensity is reduced and performance is improved during a 3-hour period of time prior to the onset of melatonin secretion (approximately 18:00h-21:00h) known as the 'wake maintenance zone'.[73]

A progressive change associated with the time spent awake is typically superimposed on the circadian rhythms of neurobehavioral performance.[74] When total sleep deprivation is extended for several days, the detrimental effects on alertness and performance increase, and although the circadian process can mitigate some of the effects of sleep loss during times of the circadian peak in alertness, it is overlaid on a continuing change reflecting increasing homeostatic pressure for sleep.

Sleep Inertia

Sleep inertia describes the confusion, disorientation, tendency to fall back asleep and decrease in alertness that occurs immediately after waking from sleep.[75-79] When comparing cognitive performance immediately upon awakening after an 8-hour night of sleep to cognitive performance after one night of total sleep deprivation, Wertz and colleagues found that impairment from sleep inertia was more severe than impairment from sleep deprivation.[79] Although it is believed that sleep inertia always occurs upon awakening, the magnitude and duration of its effect on performance depends on many factors including prior sleep duration, recent sleep history, timing of sleep and wake, and the sleep stage immediately prior to awakening.[80-82] The effects of sleep inertia on alertness and sleep propensity are more pronounced when the sleep episode is preceded by a history of sleep deprivation[83] or during the circadian nadir,[83,84] and when the sleeper is aroused from slow-wave sleep (SWS).[85,86]

Time-on-Task Effect

The time-on-task effect reflects the decrease in performance over time during a cognitively-demanding task.[87] Originally, researchers thought this phenomenon reflected boredom or decreased motivation;[87,88] however, now it is believed that the cumulative increase in effort required to perform a task for an extended period of time depletes limited cognitive resources.[89-91] As the duration of the task increases, there is a progressive increase in errors and reaction times as well as greater variability in performance;[92-95] thus, the longer an individual is required to perform a task, the more performance is negatively affected. The time-on-task effect is amplified during extended wakefulness due to sleep loss as well as during the biological night due to circadian rhythmicity.[96-100] Taking a break to rest (with or without sleep) or performing a different task replenishes cognitive resources and restores performance.[101]

Effects of Caffeine on Neurobehavioral Performance and Physiological Measures

Several experimental studies of healthy adults have investigated the efficacy of *acute* caffeine administration in counteracting the decline in neurobehavioral performance during extended wakefulness or at certain times of day using well-controlled double-blind designs. When performance was assessed during a 29-64 hour period without sleep and compared to the performance of a placebo control group, caffeine administration increased sleep latency, improved the ability to stay awake, prevented slowing of reaction times, and reduced the number of lapses in attention.[102-111] The efficacy of caffeine in producing these effects is dose-dependent[106,108,112] with higher doses (200 and 600 mg) producing better performance. However, more side effects (e.g., feelings of jitteriness, abdominal pain and nausea) have been reported after the ingestion of higher doses of caffeine (600 mg) compared to lower doses.[111] Caffeine administered in the early morning,[113-117] afternoon,[118,119] or overnight[120-122] to counteract circadian-related performance decrements also increased alertness and improved neurobehavioral functioning compared to placebo treatment.

In order to assess the *cumulative* effects of caffeine administration during extended wakefulness on various aspects of cognitive performance, sleep and sleep propensity, two studies administered a low dose of caffeine at a high frequency (0.3 mg/kg per hour). Wyatt and colleagues (2004)[123] used a forced desynchrony protocol to examine the sleep homeostatic and circadian effects of caffeine on performance separately. Subjects (16 healthy men) were placed on a 42.85 hour ‘day’ which included a 28.57 hour wake period followed by a 14.28 hour sleep period for 14 ‘days’ (i.e. 25 24-hour days) and were randomized to receive either placebo or caffeine. Subjects in the caffeine group exhibited fewer unintentional sleep onsets and better performance on cognitive throughput and attention tasks during the scheduled periods of extended wakefulness (28.57 hours) and during circadian troughs in alertness.[123]

In a double-blind study, Dinges and colleagues[124,125] also administered a sustained low-dose of caffeine (0.3 mg/kg per hour) and used a multiple-night total sleep deprivation paradigm in order to compare the effects of caffeine with or without periodic naps (NAP, 2 hour naps every 12 hours) on a range of cognitive performance outcomes. Subjects (58 healthy men) experienced three baseline nights of sleep followed by 88 hours of extended wakefulness (i.e., 3 nights of total sleep deprivation [TSD]) and 1-2 nights of recovery sleep (Figure 1). Subjects were randomized to one of four conditions: TSD with placebo, TSD with caffeine, NAP with placebo and NAP with caffeine. Caffeine or placebo was administered every hour via a pill with administration beginning during hour 22 (and continuing through hour 88) of TSD. Subjects were informed that each pill could be either placebo or caffeine (although in reality, all pills in a given condition were the same—i.e., either always placebo or always caffeine). Similar to findings in the Wyatt et al study,[123] plasma caffeine concentrations rose in an exponential saturating manner during drug administration[125]; however, there were marked individual differences in response to caffeine administration (unpublished findings, Figure 2). The maximum concentration (C_{Max}) of

plasma caffeine ranged from 2.0–9.4 mg/l among subjects, despite the fact that they remained in a controlled environment, were under the constant supervision of laboratory and hospital staff, were relatively sedentary during the study and consumed an isocaloric, caffeine-free diet. Possible mechanisms for these individual differences in response to caffeine are discussed below. Caffeine administration did not affect heart rate (data not shown), but increased core temperature (measured rectally; Figure 3) and plasma noradrenaline levels (Figure 4) compared to placebo administration (unpublished findings), consistent with the reported physiological effects of caffeine.[24,25]

It is well established that neurobehavioral performance on tests of attention, cognitive throughput and memory worsens following sleep deprivation. Consistent with other studies,[126] we found that sustained low-dose caffeine ingestion significantly attenuated decrements in reaction time and number of lapses in attention on the Psychomotor Vigilance Test (PVT);[127] however, this effect became less potent as the hours of extended wakefulness increased (unpublished findings, Figures 5A and 5B). Caffeine did not, however, significantly improve cognitive throughput as measured by the Digit Symbol Substitution Test[128] or working memory as measured by the Probed Memory Recall Task[129] (unpublished findings, Figures 5C and 5D). Notably, a 2-hour nap every 12 hours during the 88-hour sleep deprivation phase of the experiment, in combination with double-blind caffeine administration, improved attention, cognitive throughput and memory. Moreover, this effect lasted throughout the sleep deprivation period (unpublished findings, Figure 5).

Additionally, in this experiment[124,125] caffeine affected the number of times subjects experienced sleep attacks (i.e., fell asleep for 30 seconds without spontaneous recovery while performing the PVT). Although caffeine reduced the total number of sleep attacks, a 2-hour nap opportunity every 12 hours, with or without caffeine ingestion, significantly reduced the number of sleep attacks and the percent of subjects experiencing a sleep attack, and extended the number of waking hours until the first sleep attack (unpublished findings, Table 1).

Interestingly, in addition to the aforementioned effects, caffeine attenuated the typically observed decreases in cognitive performance upon awakening from nap sleep (i.e., sleep inertia). Van Dongen and colleagues (2001)[125] measured PVT performance immediately before and after five 2-hour nap opportunities among subjects receiving either placebo or caffeine during 88 hours of extended wakefulness. In the placebo condition, the number of lapses in attention was higher and response speed was slower during the test bout immediately following the nap compared to performance on the two test bouts prior to the nap. In the caffeine condition, the number of lapses and response speed during the test bout immediately following the nap were slightly improved and not significantly different from performance during the two test bouts prior to the nap;[125] thus, caffeine eliminated the effect of sleep inertia on alertness (Figure 6). Consistent with this finding, Newman et al (2013)[130] found that caffeine administration (using caffeinated gum) attenuated the effect of sleep inertia on performance when subjects are aroused after 1 and 6 hours of overnight sleep, and Hayashi et al (2003)[131] found that caffeine administration (using 100 ml of coffee) attenuated the effect of sleep inertia on performance following an afternoon nap.

Van Dongen and colleagues also assessed the effect of caffeine administration on sleep physiology during nap sleep.[125] Subjects in the NAP condition were provided with an opportunity to nap for 2 hours from 14:45h-16:45h and from 02:45h-04:45h during the 88-hour period of extended wakefulness; only naps (n=5) that occurred after pill administration began were used for analyses (Figure 1). During nap sleep, sleep latency was significantly longer (by 9.7 minutes) and rapid eye movement (REM) sleep duration was reduced (by 5.2 minutes) in the caffeine condition compared to the placebo condition,[125] consistent with a large amount of data on the inhibitory effects of caffeine on sleep onset and depth. Non-REM (NREM) sleep duration was reduced in only the first nap following pill administration and NREM slow-wave energy was reduced in only the first and second naps following pill administration in the caffeine condition compared to the placebo condition.[125] Thus, as hours of wakefulness increased across protocol days, the increased pressure for sleep superseded caffeine's disruptive effects on sleep.

When assessing alertness across the work day, high levels of caffeine consumption produced greater alertness, an attenuated slowing of reaction time, fewer cognitive failures, and a reduced risk for work-related accidents.[132] Laboratory studies have also shown that caffeine administration improved performance on long-duration tests of attention,[95,133,134] reduced impairment (e.g., lane shifting) during 1-2 hours of continuous driving in a driving simulator,[135,136] and attenuated fatigue induced by the time-on-task effect.[7,99,113]

Effects of Caffeine on Circadian Rhythms

While much is known about the effects of caffeine on sleep and neurobehavioral performance deficits due to sleep loss, far less is known about caffeine's effects on circadian rhythms, with the vast majority of data obtained from nonhumans. Caffeine has been reported to phase shift the melatonin rhythm in chick pineal cells in a phase-dependent manner similar to the effects of light,[137] and to phase shift the temperature rhythm of rats.[138] In hamsters, caffeine attenuated phase shifts induced by wheel running.[139] Mechanistically, in rodents, caffeine may act directly on the SCN to alter circadian phase.[140-142] This finding would be consistent with reports that the adenosine A_1 receptor modulates light-induced phase shifts, protein expression in the SCN, and SCN field potential amplitude following optic nerve stimulation.[143-145] Caffeine also lengthened the circadian period in both the fungus Neurospora[146] and in mouse cell lines and cultured liver explants,[141] where caffeine lengthened the circadian period of clock gene expression. In intact mice, under ad libitum feeding conditions,[147] caffeine modified clock gene expression in the liver and jejunum.

By contrast, in humans, few data on the circadian effects of caffeine are available. In a forced desynchrony protocol, caffeine did not significantly affect circadian period compared to placebo.[123] However, in a modified constant routine protocol, caffeine decreased nighttime melatonin levels, attenuated the normal decrease in body temperature, and phase delayed the temperature rhythm during 45.5 hours of extended wakefulness.[148] It is unknown, however, whether these effects last beyond the day of measurement to subsequent days. Appropriately timed doses of caffeine, given in the evening, may be able to phase delay the endogenous circadian pacemaker in humans, similar to light. However, further research is warranted, including the development of phase-response curves using different

physiological doses of caffeine. Such information would be valuable given caffeine's extensive use in situations of circadian misalignment including night shift work and jetlag.

Individual Differences in Response to Sleep Deprivation and Genetic Contributors

Individual differences in response to caffeine have long been recognized (see next section), and more recently, stable individual differences in response to sleep deprivation have also been confirmed, posing the question of whether individual differences in the two response domains share a common biological basis. We demonstrated experimentally that differential cognitive vulnerability to sleep deprivation is stable and trait-like, strongly suggesting a genetic component.[149,150] In experiments involving repeated exposure to sleep deprivation in the same subjects, the intraclass correlation (ICC) coefficient, which expresses the proportion of variance that is explained by systematic inter-individual variability, revealed that trait-like responses accounted for 58-68% of the overall variance in PVT performance lapses of attention.[150,151] Thus, healthy adults who had high lapse rates during sleep deprivation after one exposure had high lapse rates during a second exposure, and those with low lapse rates were similarly consistent.[150,151] Because high ICCs were evident when subjects were exposed to 36h of total sleep deprivation repeatedly under markedly different state conditions (6h versus 12h sleep time per night for 7 days before the total sleep deprivation protocol), marked differences in neurobehavioral vulnerability to sleep deprivation can be characterized as phenotypic (trait-like, rather than state-specific).[150,152]

A recent study by Kuna et al. (2012)[153] using monozygotic (MZ) and dizygotic (DZ) twin pairs confirmed the trait-like feature of neurobehavioral vulnerability to sleep loss. The authors found that the ICC for PVT lapses over 38h of total sleep deprivation in MZ twin pairs was 56.2% whereas it was only 14.5% for DZ twins, showing that behavioral impairment produced by sleep deprivation is a highly heritable trait (a heritability, or the proportion on variance in a trait due to genes, of .83). Rupp et al. (2012)[154] found in a small sample of healthy adults that those who had greater neurobehavioral deficits in response to acute total sleep deprivation also had greater deficits in response to chronic sleep restriction, indicating that the type of sleep deprivation did not alter one's neurobehavioral vulnerability to sleep loss, though more extensive studies are needed to confirm and extend this preliminary finding.

The discovery that more than 50% of the variance in performance deficits due to sleep loss is trait-like resulted in a search for markers to predict more- versus less-vulnerable individuals. Thus far, these phenotypic differences in neurobehavioral responses to sleep deprivation have not been predicted by demographic factors (e.g., age, sex, IQ), baseline cognitive performance, aspects of habitual sleep timing, circadian phase preference, or any other investigated factor.[150,155] The apparent stability of these responses over time, as well as their high heritability, suggest an underlying genetic component. To this end, a number of studies have investigated the effects of genetic polymorphisms on individual differences in neurobehavioral vulnerability to sleep loss. Polymorphisms studied have included those in the circadian gene *PERIOD3* (*PER3*),[47,156-160] the human leukocyte antigen (HLA) gene

*DQB1*0602*,[161] the *Catechol-O-Methyltransferase* (*COMT*) gene,[162,163] the *Brain-Derived Neurotrophic Factor* (*BDNF*) gene,[164] and various adenosine genes.[160,165-168]

Individual Differences in Response to Caffeine and Genetic Contributors

It has long been established that there are marked individual differences in sensitivity to caffeine.[169] Twin studies have indicated substantial heritability in caffeine consumption, heavy caffeine use, caffeine intoxication, caffeine tolerance, and caffeine withdrawal, with heritabilities ranging from 0.35 to 0.77 for these measures.[170-172] Similarly, Luciano et al. (2007)[173] found substantial heritability (0.40) in caffeine's effects on sleep disturbance. In recent years, the genetic basis of individual differences in response to caffeine has been investigated; findings indicate that both pharmacodynamic (drug-receptor) and pharmacokinetic (metabolic) polymorphisms are associated with such differences.[174]

Variations in caffeine metabolism, accomplished mainly in the liver by the CYP1A2 enzyme, underlie some of the individual differences in response to caffeine. A polymorphism in the CYP1A2 gene that decreases enzyme inducibility results in slower metabolism.[175] Indeed, slower caffeine metabolism is associated with a higher prevalence of this polymorphism in Asian and African populations (vs. Caucasians), and in women compared to men.[175]

Of interest, some of the same polymorphisms associated with individual differences in response to sleep loss (reviewed above) also appear to play a role in individual differences in response to caffeine. Two examples include polymorphisms found in the *Adenosine A2A receptor* (*ADORA2A*) gene and in the *Catechol-O-methyltransferase* (*COMT*) gene. A polymorphism in the *ADORA2A* gene has been associated with caffeine consumption[176], caffeine-induced anxiety[177-179] and self-identified caffeine-sensitive individuals.[166] This variation also contributes to individual differences in the effects of caffeine on subjective and objective sleep-related outcomes.[166,180]

Caffeine stimulates adrenomedullary secretion of the *catechol-O-methyltransferase* (*COMT*) enzyme.[181] A Val158Met polymorphism[181] in the *COMT* gene was associated with higher risk of acute myocardial infarction in middle-aged males who were heavy caffeine users (coffee drinkers) and had the lower, but not the higher activity *COMT* allele. We found that higher *COMT* activity subjects showed differentially smaller SWS increases and smaller reductions in stage 2 sleep during chronic sleep restriction, more stage 1 sleep across nights, and shorter baseline REM sleep latency—all indicative of a lower sleep homeostatic drive.[163] By contrast, lower *COMT* activity subjects showed significantly less stage 1 sleep and a longer REM sleep latency at baseline and during chronic sleep restriction—indicative of a greater sleep homeostatic drive.[166] Future studies should examine individual differences in caffeine response in the high and low *COMT* activity genotypes undergoing sleep loss.

Conclusion

The increasing prevalence of adults experiencing total sleep deprivation or chronic sleep restriction due to work, lifestyle, or biological factors has undoubtedly contributed to a growing market for CCEP that can increase alertness and mitigate declines in performance,

especially for those individuals who are vulnerable to sleep loss. All of the top-selling energy drinks contain the central nervous stimulant caffeine, which can (within limits and to varying degrees) be an effective countermeasure for sleepiness and fatigue related to sleep loss, circadian rhythmicity, sleep inertia and time-on-task. The effects of other ingredients in CCED (e.g. taurine, glucose and B-vitamins) on cognitive and physical performance are reviewed elsewhere in this issue, but further research is required in this area.[3]

The U.S. Food and Drug Administration (FDA) has classified caffeine as 'generally regarded as safe' so its use as an additive is exempt from the Federal Food, Drug, and Cosmetic Act tolerance requirements.[15] However, caffeine may be unsafe and its effects difficult to predict at higher doses, especially for individuals with certain genetic polymorphisms or with specific medical conditions (e.g., heart conditions, hypertension, diabetes, gastrointestinal issues). Recently, the FDA has expressed concerns over possible adverse effects related to cumulative caffeine intake since caffeine is added to an increasing number of products.[182] As discussed in this review, we found that chronic administration of a low dose (0.3mg/kg per hour) of caffeine during the final 66 hours of 88 hours of sleep deprivation (with and without naps) led to increased core temperature and elevated plasma noradrenaline. Interestingly, when subjects were asked whether the pill they were administered in the previous hour contained caffeine or placebo, accurate perceptions were not significantly better than chance in both placebo and caffeine groups.[125] In addition to being unable to detect small frequent doses of ingested caffeine, individuals often do not realize how many foods/drinks contain caffeine and underestimate how much caffeine they consume.[183] Future studies should thoroughly investigate the physiological effects of cumulative caffeine intake in large, diverse populations.

It is important for caffeine consumers to understand that caffeine at any dose is not a chemical substitute for adequate healthy sleep. As the experimental results summarized in this review indicate, when the pressure for sleep is high, caffeine has little effect on preventing performance deficits and sleep attacks that can pose serious risks, especially in safety-sensitive areas (e.g., motor vehicle operation). Dinges and colleagues[77,184] as well as others[83,185] have shown that naps are effective countermeasures that prevent performance decline in situations of increased sleep propensity and decreased alertness. Although naps are effective and lack the physiological side effects of caffeine, one unwanted side effect is subsequent sleep inertia, which can be reduced by caffeine. Thus, brief naps in combination with properly-dosed and well-timed energy products containing caffeine may provide the most benefit.

Effective and safe use of caffeine to promote alertness requires an appreciation of one's responses to the stimulant (e.g., acute and chronic effects). After ingestion, peak blood concentrations of caffeine are reached within one hour and the half-life of caffeine is about 5-6 hours;[186,187] however, as described above, there are significant individual differences in the response to caffeine, with half-life ranges varying between 2.5-10 hours (this range is even larger among individuals who are pregnant, are taking antidepressants, or have liver disease).[188] If ingested in the evening, at night or prior to daytime naps, caffeine can disrupt sleep[189-194] and perhaps phase delay circadian rhythms and thereby contribute to sleep loss and subsequent decreases in alertness. Finally, many adults develop tolerance to caffeine, so

limiting its use may enhance its efficacy.[195-198] If caffeine is to be used effectively to improve performance, it is wise to avoid consuming it when nonessential (i.e., as a readily available food/drink), and instead ingest it as a countermeasure only when needed.

Due to the 24-hour nature of modern society, situations leading to 'low-energy' will invariably arise and there is a need for effective countermeasures to maintain performance, especially where decrements in performance pose a high-risk for human safety. For healthy adults, CCED may be an effective and generally safe option when used strategically and especially in combination with naps.

Future Research Directions

As summarized in this review, a significant amount of research has characterized the effects of caffeine on neurobehavioral performance during situations of 'low-energy'; however, the effects of caffeine on energy balance are less well understood. In addition to causing a decrease in alertness and an increase in fatigue, sleep loss and circadian disruption (due to habitual short sleep durations and/or shift work) have also been associated with weight gain and greater risk for obesity.[199-201] We have recently shown that sleep restriction in the laboratory leads to weight gain and increased caloric intake particularly during late-night hours.[202] It remains unclear how CCEP affect weight gain, metabolism and appetite under normal or 'low-energy' conditions. Caffeine has been associated with increased energy expenditure and lipolysis,[203] greater satiety,[204,205] and reduced weight gain[206,207] suggesting its possible effectiveness for weight management. Unfortunately, caffeine is often ingested as part of sugar-sweetened beverages—all of the top-selling CCED contain sugar (although some brands offer sugar-free options) — which may actually promote weight gain and obesity.[208] Future studies are critically needed to examine the efficacy of caffeine for attenuating the energy balance effects of sleep loss and circadian misalignment, particularly in light of our nation's growing obesity epidemic.

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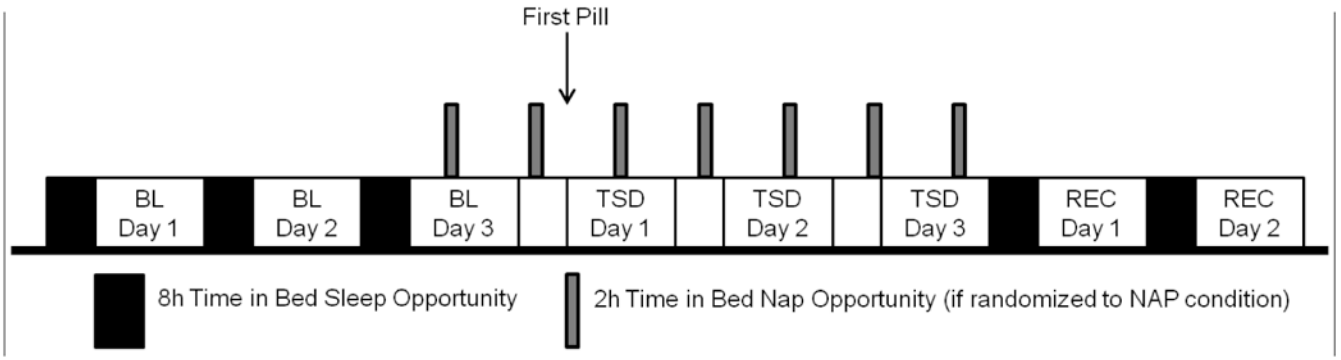

Figure 1. Overview of Chronic Caffeine Study Protocol

Fifty-eight healthy male subjects (mean age, 29 years) with a history of moderate caffeine intake were admitted to the Hospital of the University of Pennsylvania. Subjects did not use any caffeine, alcohol, tobacco or other medications in the two weeks prior to or during the experiment. The laboratory experiment began with one adaptation day and two baseline (BL) days with bedtimes from 23:30h-07:30h. Subjects then underwent 88 hours of extended wakefulness (i.e. three nights of total sleep deprivation; TSD). If subjects were randomized to the NAP condition, they were provided with seven 2-hour nap opportunities scheduled every 12 hours from 14:45h-16:45h and from 02:45h-04:45h. Starting 22 hours into the 88-hour period of extended wakefulness, subjects received a pill containing either 0.3 mg/kg caffeine or placebo every hour (except during naps). After the 88-hour period of extended wakefulness, subjects remained in the laboratory for 1-2 nights of recovery sleep.

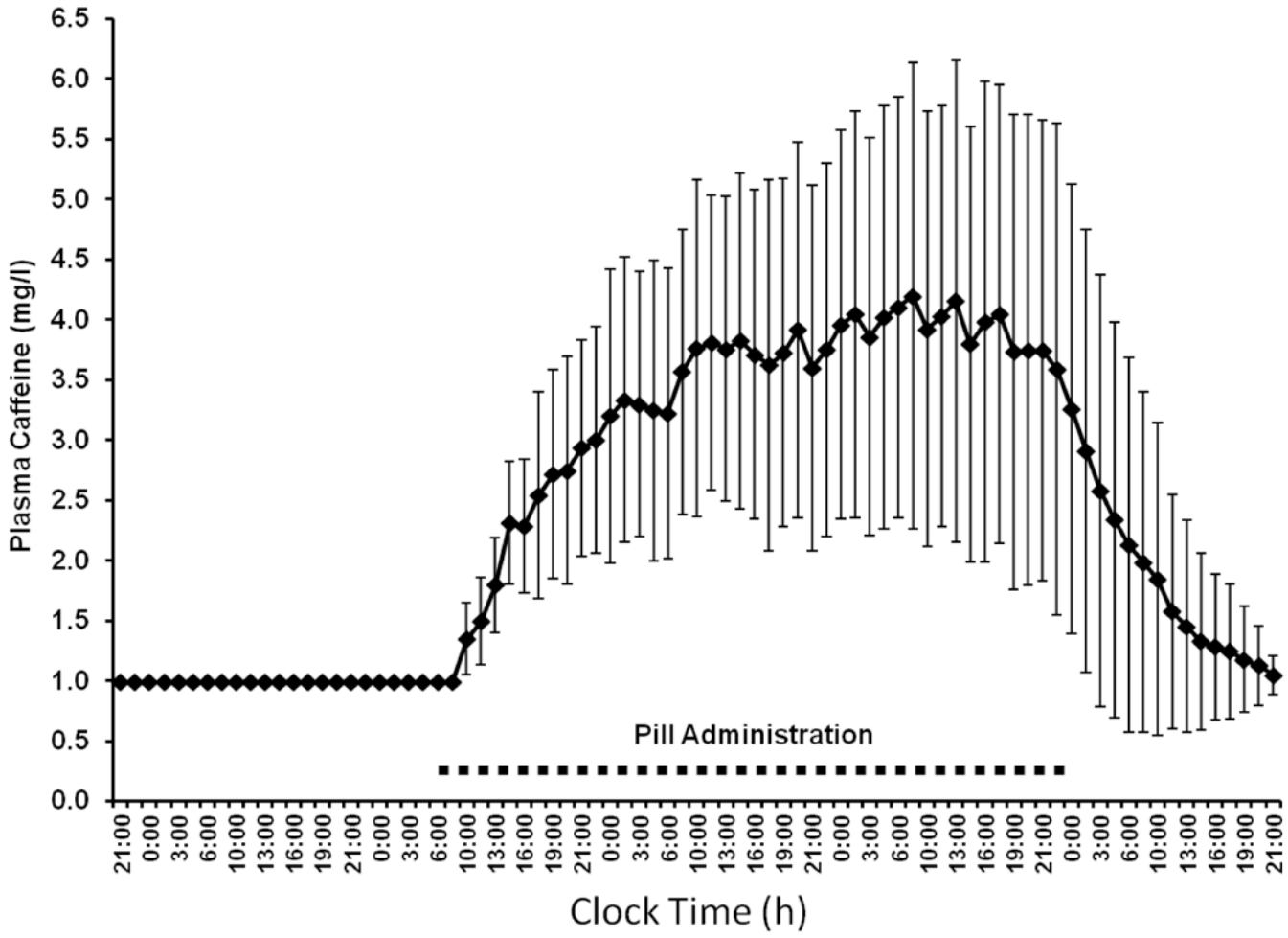

Figure 2. Plasma Caffeine Levels among Subjects Administered Caffeine during Extended Wakefulness

Subjects were administered placebo or caffeine (0.3 mg/kg) every hour from hours 22-88 of extended wakefulness (i.e. they received 66 pills). For example, a 75 kg subject would have received 22.5 mg of caffeine per pill which results in a total cumulative dose of 1485 mg caffeine (540 mg caffeine per day). Blood samples were taken via an indwelling intravenous catheter for assessment of plasma concentrations of caffeine at 90 minute intervals. Caffeine levels were assessed using standardized radioimmunoassay techniques. Caffeine levels rose steadily within 3.25 hours of the first administration. There were marked individual differences in plasma caffeine levels (indicated by SD and the C_{Max} range: 2.0-9.4 mg/l). Following the end of administration, there was a steady decline in plasma caffeine levels. Data shown as Mean ± SD for n=25 subjects receiving caffeine (unpublished findings).

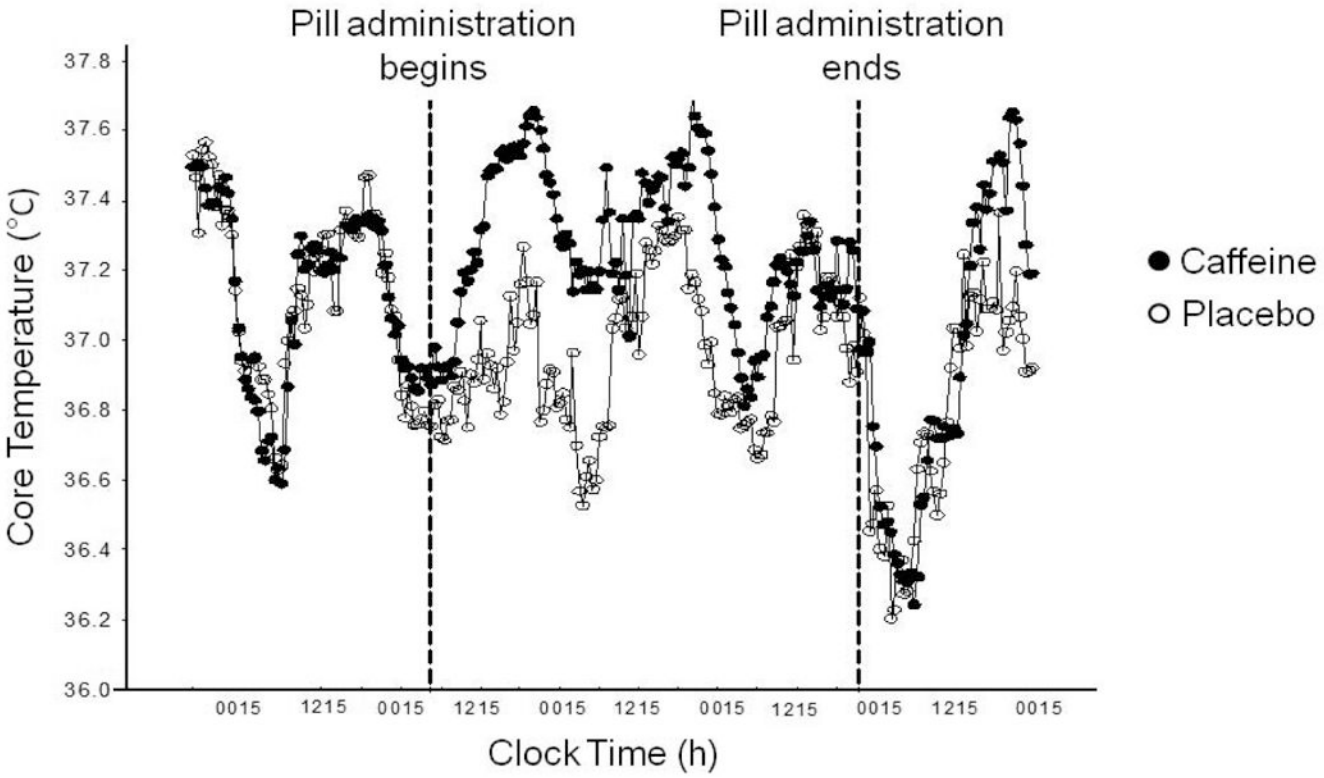

Figure 3. Core Temperature among Subjects Administered Caffeine or Placebo during 88 hours of Extended Wakefulness

Core temperature was monitored continuously from Baseline Day 3 until the end of the 88 hour period of extended wakefulness (total sleep deprivation). Core temperature was sampled at 2-minute intervals using a Steri-Probe 491B rectal thermistor (YSI, Yellow Springs, OH) connected to an Actillume ambulatory recording system (Ambulatory Monitoring, Inc., NY). Core temperature was significantly higher in the caffeine group relative to the placebo group 4-22 hours after the first caffeine administration ($p < 0.0001$). As expected, both groups demonstrated a significant circadian rhythm in core temperature. Data presented as raw means (unpublished findings).

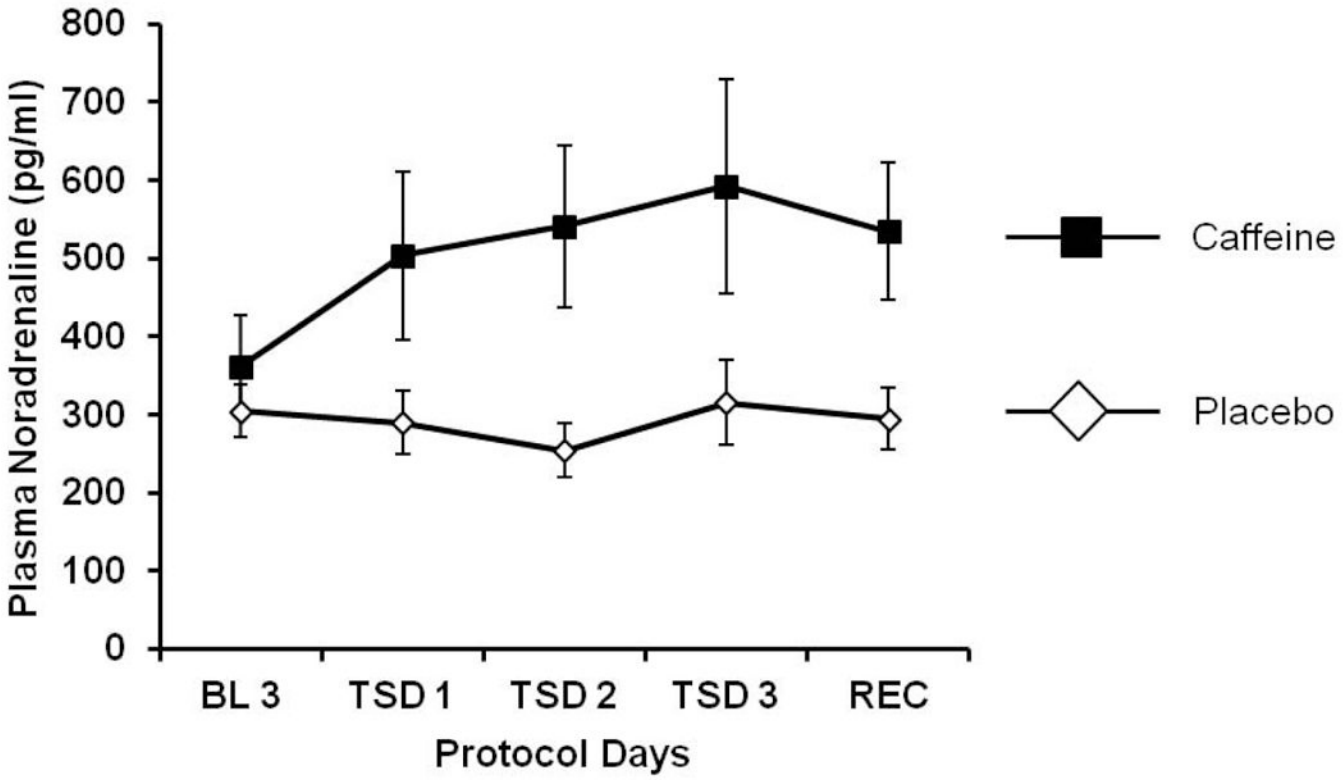

Figure 4. Plasma Noradrenaline Levels among Subjects Administered Caffeine or Placebo during 88 hours of Extended Wakefulness

Plasma noradrenaline levels were assessed in blood samples taken every 90 minutes beginning on Baseline Day 3 (BL 3), through the 88 hours of extended wakefulness (total sleep deprivation; TSD1-3) and ending during the first recovery day (REC). Although sleep loss did not significantly affect noradrenaline levels, sustained low-dose caffeine administration significantly increased plasma noradrenaline levels compared to placebo administration ($p=0.016$). There were notable individual differences in plasma noradrenaline levels in response to caffeine (the standard deviation on TSD Day 3 was much larger among subjects in the caffeine group (SD=389.1) compared to subjects in the placebo group (SD=161.7). Data shown as Mean ± SEM for n=17 subjects in the TSD Condition (unpublished findings).

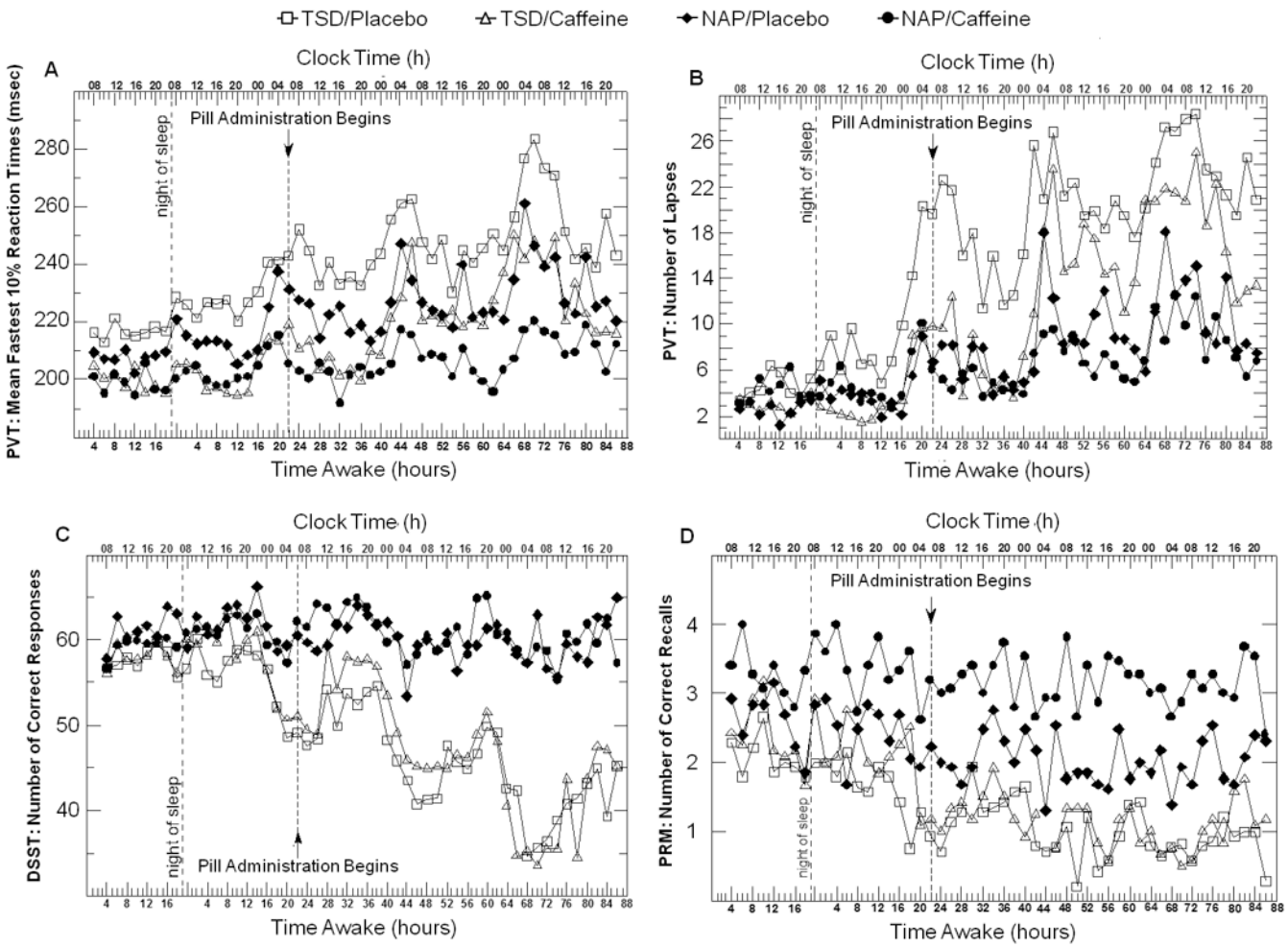

Figure 5. Neurobehavioral Performance across 88 hours of Extended Wakefulness

Subjects were randomized to one of four conditions during 88 hours of extended wakefulness: No nap opportunities with placebo treatment (TSD/Placebo), No nap opportunities with caffeine treatment (TSD/Caffeine), 2-hour nap opportunities every 12 hours with placebo treatment (NAP/Placebo) and 2-hour nap opportunities every 12 hours with caffeine treatment (NAP/Caffeine). Standardized measures of performance were collected every 2 hours using a 30-minute computerized assessment battery. This test battery included the Psychomotor Vigilance Test (PVT)[127], the Digit Symbol Substitution Test (DSST)[128] and the Probed Recall Memory Task (PRM)[129]. The PVT is a simple reaction time test of behavioral alertness that is free of a learning curve and is highly sensitive to sleep deprivation. During the DSST, subjects are presented with nine different symbols which each correspond to a number (1-9) and must type in the correct number when each symbol that appears on the screen. In the PRM task subjects are presented with a list of six word pairs for 30 seconds and then after taking another test for 10 minutes, subjects are given one word from each set of pairs and have 2.5 minutes to fill in the complementary word. Sleep deprivation led to significantly slower reaction times (A) and an increase in the number of lapses in attention (B) on the PVT, a decreased number of correct responses on the DSST, reflecting slowed cognitive throughput (C) and a decrease in the number of words

correctly recalled on the PRM, indicating impaired memory (D). Caffeine administration improved reaction time and reduced attentional lapses during the first 22 hours of administration (hours 24-46 of extended wakefulness; $p < 0.05$) but had no significant effect on DSST or PRM performance. Naps in combination with caffeine improved performance on all three tasks across the entire period of extended wakefulness. Data presented as raw means (unpublished findings).

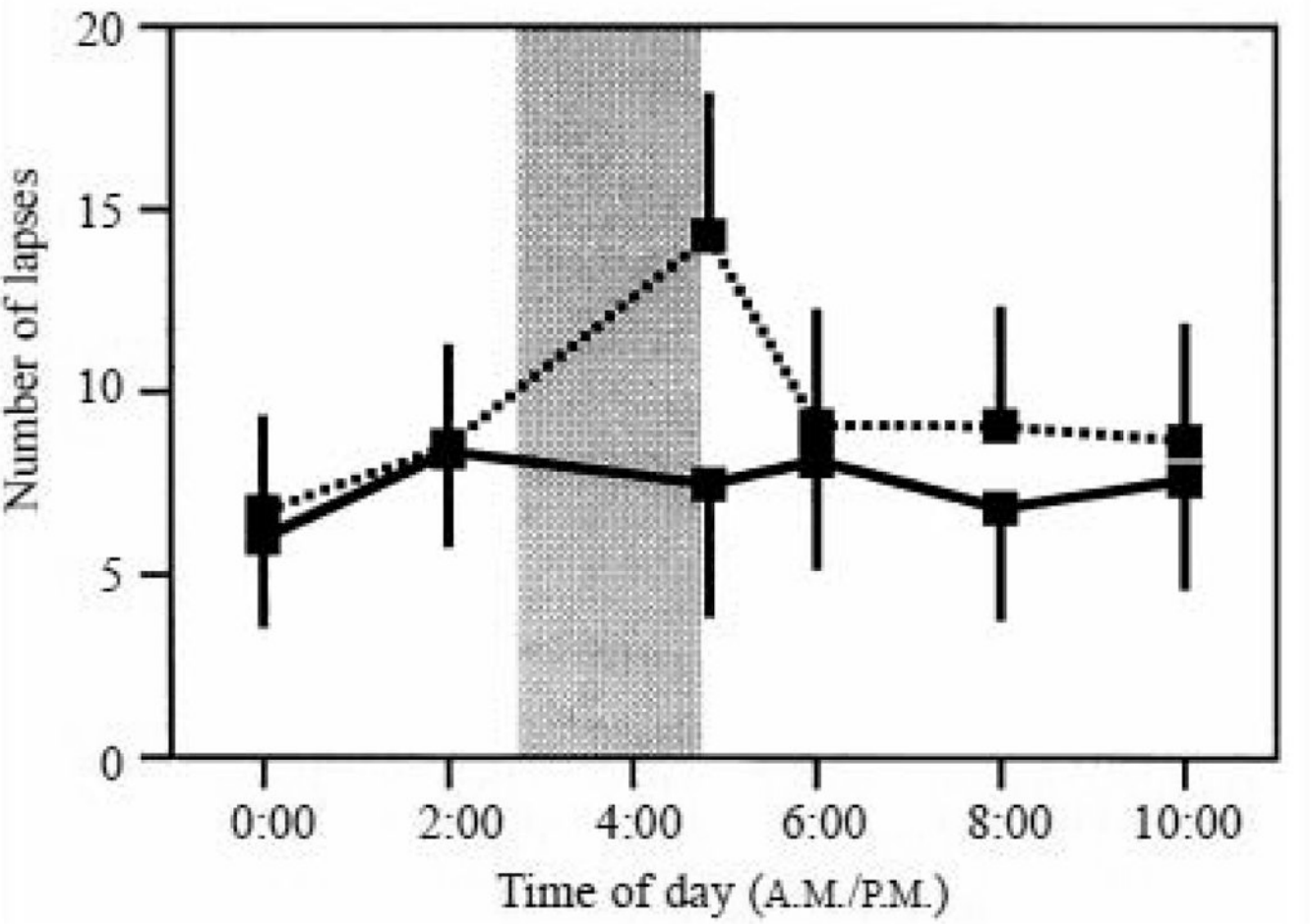

Figure 6. Caffeine and Sleep Inertia

Performance lapses (> 500 ms reaction time; total per test bout) on the PVT 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 AM and PM times of day; naps (gray bar) took place from 14:45h-16:45h and from 02:45- 04:45h. Sleep inertia (increases in the number of PVT lapses) was consistently observed immediately after each nap in the placebo condition, but not in the caffeine condition. Data presented as Mean ± SEM for n=28 subjects in the NAP condition. (Figure reprinted with permission from Van Dongen et al., 2001, *Sleep*).

Table 1

Effect of placebo versus caffeine treatment on sleep attacks* while taking the Psychomotor Vigilance Test during either 88 hours of total sleep deprivation (TSD) or 88 hours of extended wakefulness with 2-hour nap opportunities every 12 hours (NAP)**

Condition	Total Number of Sleep Attacks	Subjects with > 1 Sleep Attack (% of subjects in that condition)	Wake Time (hours) to First Sleep Attack
TSD/Placebo	173	8 (57%)	23
TSD/Caffeine	59	5 (42%)	23
NAP/Placebo	3	2 (15%)	72
NAP/Caffeine	3	2 (13%)	50

* falling asleep for 30 seconds without spontaneous recovery

** (unpublished findings)