33
Caffeine, Sleep, and Quality of Life

Monicque M. Lorist and Jan Snel

Summary Caffeine is regarded as a mild stimulant acting on the central nervous system that is responsible for a significant portion of the behavioural and physiological effects of coffee and tea. Motives why people take caffeine are reflected in consumption patterns. Early in the morning caffeine might help to wake up, whereas during the day it is an aid to stay awake or counteract fatigue. The intake of caffeine shortly before sleep might affect sleep characteristics, especially if high doses of caffeine are used. Moreover, these disturbances of sleep might result in tiredness in the morning. Caffeine is frequently used as a countermeasure for fatigue and sleepiness. During sub-optimal circumstances such as working night shifts and sleep deprivation it maintains performance and wakefulness at satisfying levels. These effects of caffeine depend largely on its antagonistic actions on the A_{2A} adenosine receptor. Simple task performance seems in particular sensitive to caffeine. Part of the caffeine effects might be due to withdrawal reversal, although caffeine is stimulating in non-withdrawn subjects, as well. In addition, in habitual users, there is no complete tolerance to the effects of caffeine.

Keywords Caffeine · wakefulness · sleepiness · night shift · sleep deprivation · withdrawal · fatigue

Learning objectives:

- Caffeine increases physiological arousal by antagonizing the effect of adenosine.
- Caffeine is effective in maintaining performance and wakefulness at satisfying levels during sub-optimal circumstances, occurring during the normal sleep–wake cycle, and in sub-optimal periods, occurring after disturbances of the normal sleep–wake rhythm (e.g., working night shifts and sleep deprivation).
- Simple task performance is more sensitive to caffeine than complex task performance, involving higher level cognitive control processes.
- A modest disturbance of sleep quality is found with caffeine taken shortly before sleep.
- Stimulating caffeine effects have been found in both non-withdrawal and caffeine-withdrawn subjects.
- Part of the caffeine effects might be ascribed to relief of withdrawal.
- Habitual caffeine consumers do not develop complete tolerance to the effects of caffeine.

Introduction

Caffeine is a widely used alkaloid mainly derived from coffee or tea. The popularity of caffeine may be related to its stimulating effect on the central nervous system. There is indeed a substantial amount of evidence illustrating that caffeine increases subjective energy and alertness (1–6). Moreover, caffeine is legally available and consumption is socially accepted. It is, therefore, no surprise that caffeine is frequently used as a countermeasure for fatigue and sleepiness related to working night shifts and sleep deprivation.

The relation between caffeine, sleep, and performance was and still is the topic of many studies (7–10). Do the results of these studies justify the use of caffeine to postpone sleep and improve wakefulness? Also, sleep is important for cognitive performance. Therefore, if caffeine keeps people awake, what about its effects on sleep?

Caffeine is responsible for a significant proportion of the behavioural and physiological effects of coffee, tea, cocoa and chocolate. After oral ingestion, caffeine is rapidly and almost completely (99%) absorbed from the gastrointestinal tract into the bloodstream (11, 12). It is widely distributed throughout the body tissues, and passes through all biological membranes, including the blood–brain barrier and the

From: J. C. Verster et al. (eds.): *Sleep and Quality of Life in Clinical Medicine*

placental barrier. Peak plasma concentrations are reached in about 30–60 min after ingestion. The half-life of caffeine is approximately 3–5 h, although individual clearance rates vary tremendously. For example, the clearance rate is speeded up with 30–50% by nicotine, and doubled in woman taking oral contraceptives. Caffeine has hardly any side-effects, and it has a low profile as a drug of abuse (13).

Caffeine effects, at doses comparable with those of normal human intake, are primarily related to its blocking of the A_1 and A_{2A} subtypes of the adenosine receptors (12, 14, 15). Adenosine is an inhibitory neuromodulator involved in sleep–wake regulation (16, 17). Extra-cellular concentrations of adenosine in the basal forebrain cholinergic region were, for example, found to increase during spontaneous wakefulness and during sustained, prolonged wakefulness, whereas a slow decline in concentration was observed during recovery sleep (17). Caffeine-induced wakefulness depends in particular on its antagonistic actions at the A_{2A} receptor subtype (18).

Normal Sleep–Wake Cycle

During the day, natural fluctuations of arousal and sleepiness exist. The desire to increase arousal at certain times of day may be a factor influencing the amount of caffeine intake. In a review by Bättig (19), this hypothesis was actually supported; Bättig reported that 27% of 20- to 40-year old women drank coffee at wake-up, 73% at breakfast, 60% at the morning break, 23% late in the morning, 52% with the lunch, 48% at the afternoon break, 32% in the late afternoon, 18% at dinner, and 43% after dinner. To assess diurnal patterns in caffeine consumption, Brice and Smith (20) used a caffeine diary, a retrospective questionnaire, and a detailed personality and psychosocial profile. They found that consumption levels peaked between 8 a.m. and 12 noon and decreased thereafter. Corresponding consumption patterns were also found in 691 undergraduate students (409 women) (21). While average caffeine consumption decreased from the morning through the evening, the consumption of decaffeinated coffee increased throughout the day from hardly 1% at breakfast to 13% after dinner (19). These patterns might reflect the shift over the day in motives why people take coffee. Early in the morning caffeine is taken mainly to wake up. After a night of caffeine abstinence with a low level of arousal, caffeine can help to increase the activity of the sympathetic adrenal-medullar system. The acceleration by coffee may help to reach sooner the habitual level of functioning (22). During the day, caffeine might be of help to counteract fatigue. Fatigue is a natural consequence of many daily-life activities, which may underlie sub-optimal functioning or even human error such as found in traffic situations and professional activities. No surprise that people look for ways to compensate fatigue and sleepiness when necessary. A specific increase in sleepiness and performance decline has been found in the mid-afternoon, the so-called 'post-lunch dip of attention', which has been related to increased accident rates (23, 24). Smith (25) found in a double-blind, placebo-controlled study that a dose of 1.5 mg/kg caffeine was indeed an effective countermeasure against this post-lunch dip. Hayashi, Masuda and Hori (26) compared the effects of 200 mg caffeine, bright light (2000 l×) and face washing in combination with a short daytime nap on sleepiness. They found that the combination of caffeine and napping was the most effective in alleviating mid-afternoon sleepiness and related performance deteriorations.

Although caffeine might compensate sleepiness during daytime, it might also cause sleep disturbances, especially when taken shortly before sleep (27). Drapeau et al. (28), for example, evaluated the effects of caffeine on sleep variables in moderate caffeine users (1–3 cups a day), while they maintained their habitual caffeine consumption. Subjects received 100 mg caffeine 3 h before bedtime and another 100 mg 1 h before bedtime. Caffeine increased sleep latency, reduced sleep efficiency, the duration and amount of stage 2, and also spectral power in the delta frequencies, indicating that moderate caffeine consumers remain sensitive to the effects of caffeine despite their habitual daily intake. Alford and co-workers (29) used a 4 and an 8 mg/kg dose of caffeine to evaluate the effect on sleep quality. They found in six young healthy volunteers (aged between 21 and 25 years), who abstained from caffeine for 2 weeks, that a 4-mg/kg dose given 20 min before bedtime doubled sleep onset latency. Effects on sleep efficiency (17% decrease), the number of awakenings (7% increase), slow wave sleep (4% decrease) and non-REM sleep (8% decrease) were restricted to the higher dose of 8 mg/kg.

In general, a relative high dose of 4 mg/kg caffeine, which is comparable to normal use in everyday life, may cause only a slight postponement of falling asleep, while the effects on sleep structure remains fairly small. Åkerstedt and Ficca (30) argued that, even for doses up 6 to 7 cups a day, sleep disturbance due to caffeine ingestion in everyday situations seems small.

Orbeta and colleagues (31) examined the relation between caffeine consumption, sleep quality, and the frequency of feeling tired in the morning in a large group of students in grades 6 through 10. High caffeine intake was related to an increase in sleeping difficulties and morning tiredness. Disrupted sleep, causing morning tiredness and sleepiness during daytime were ascribed to a disrupted sleep–wake cycle due to the consumption of caffeine containing beverages till late at night. Twenty to twenty-five percent of children and adolescents report sleep disturbances, part of which might be related to caffeine intake. In 13–17 years old US children caffeine intake comes mainly from soft drinks (62%), among them energy drinks. Only one-third comes from coffee and 3% from tea (32), whereas in adults these figures are 75 and 15%, respectively (33).

'Energy' drinks not only contain different levels of caffeine but some also contain high sugar levels. Anderson and Horne

(34) examined the effects of an energy drink with low caffeine content (30 mg) and high sugar content (42 g) on afternoon sleepiness induced by restricted sleep (5 h) the night before. The performance on a vigilance task was worse after the intake of this energy drink. They concluded that it is the caffeine content of energy drinks that is effective in counteracting sleepiness.

In summary, the intake of caffeine, especially high doses, shortly before sleep might disturb sleep, causing tiredness in the morning. Moreover, habitual caffeine consumers remain sensitive to these effects of caffeine.

Irregular Sleep–Wake Cycle

Shift Work

In our 24-h economy, flex- and irregular work schedules are common. Adaptation of the circadian rhythm to night work, however, occurs only partially over time, because adjustment is severely opposed by compelling Zeitgebers such as the natural light–dark cycle, family and social activities during the day, and the forced reversal of wakefulness during daytime and sleep at night on non-working days. As expected, persons who work night shifts frequently report that sleep at daytime is disrupted and non-refreshing. In both permanent night workers and in rotating shift workers, total sleep time is reduced to about 5–6 h per day. Moreover, about 10% of shift workers suffer from 'shift-work sleep disorder' defined as a primary complaint of insomnia or excessive sleepiness when temporally coupled with a work period that occurs during the habitual sleep phase, and which is associated with increased risks for several diseases (35).

Torsvall and colleagues (36) found that 20% of shift workers fell spontaneously asleep during night shift. Such naps did not occur during afternoon or evening shifts. Especially between 3 and 6.30 a.m., people are least alert and most likely to fall asleep. Parallel to the circadian arousal rhythm, human performance shows a trough for most cognitive skills during the early morning hours. The magnitude of these performance deteriorations during night versus daytime in the laboratory ranges from 10 to 35% of the 24-h mean level of performance (37). Additionally, accidents and injuries are 1.3 times more likely to occur on a night shift than on a day shift (38). Connor and colleagues (39) showed that the risk of serious and fatal traffic accidents may even increase 5.6 times between 2 and 5 a.m., particularly when travelling between the workplace and home (40). Prevention of sleepiness related to night work is therefore of direct relevance for road safety.

Two main sources of reduced alertness and performance during nightly work hours are the disturbed circadian rhythm of sleepiness and alertness, and increasing homeostatic sleep pressure related to the period of wakefulness preceding work time. There are indications that caffeine affects the circadian rhythm of humans (41–43). Shilo and colleagues (44) examined the effects of caffeine in six volunteers who regularly consumed coffee during the afternoon and evening hours. Although subjects were unable to determine whether they had consumed regular or decaffeinated coffee during the study periods and did not report significant differences in sleep quality estimations or bedtime, caffeine increased sleep latency and affected all other sleep variables. In addition, caffeine consumption decreased secretion of melatonin. In a simulated shift work situation, the influence of 200 mg caffeine was studied in none to moderate caffeine users ($\leq$2 cups a day; aged between 19 and 36 years) (45). Work started at 5:30 p.m. and went on until 10 a.m. the next morning. During the 1-h rest period from 1:30 to 2:30 a.m., the participants performed performance tests lasting 90–95 min. Caffeine was found to be beneficial for performance during the night, which was ascribed to its lowering effect on melatonin, an endogenous regulator of the sleep–wake cycle secreted nocturnally by the pineal gland (46).

In addition to the effect of caffeine on the circadian rhythm, it has been argued that caffeine primarily promotes wakefulness by its effect on adenosine. In other words, consumption of caffeine might be responsible for the altered expression of sleep homeostatic pressure (47–49). Wyatt and colleagues (50) used a 29-day forced desynchrony protocol in which the sleep–wake cycle was scheduled to be 42.85 h, that is, far removed from the circadian range. The aim was to examine the contributions of sleep-homeostatic and circadian-timing systems in caffeine-related performance modulations. Sixteen men (aged between 18 and 30 years) consumed caffeine (0.3 mg/kg) or placebo hourly during 28.6-h wake episodes. This high-frequency low-dose caffeine was effective in countering the detrimental performance effects of extended wakefulness, which was ascribed to attenuation of the homeostatic sleep drive.

Workers nap frequently between 1.5 and 2.5 h per nap before night-shift work (51). The aim of Bonnet and Arand (52) was to compare the effect of either napping for 4 periods of 1 h each or for one 1 nap period of 4 h in combination with or without a dose of 200 mg slow-release caffeine (SRC) on alertness and performance. Caffeine in the form of SRC is valuable, because it may result in long and good-quality wakefulness not only in laboratory situations but especially in those real-life situations in which opportunities to consume caffeine may be limited. Addition and logical reasoning improved during the night after the combination of SRC and a 4-h nap before the shift. It should be noted that the use of SRC is not advisable in situations in which unexpected sleep opportunities might arise, because of its long-lasting efficacy.

Philip and colleagues (53) examined the effects of a 30-min nap taken before a drive in addition to coffee containing 200 mg caffeine or decaffeinated coffee in a real-life environment. Twelve young men (aged between 20 and 25 years) ingested caffeine 30 min before a 200-km (125 miles) driving session between 2 and 3:30 a.m. In the caffeine condition, for 75% of the participants, nighttime driving performance was similar to daytime performance as compared with 66% after the nap and only 13% in the placebo condition. Schweitzer and colleagues (54) combined caffeine (4 mg/kg) with a 2.5-h nap in both a laboratory and a field setting. They confirmed that caffeine and napping improved alertness and vigilance; however, the combination of caffeine and napping was superior to coffee or napping alone both in the laboratory and in the real-life environment.

In sum, simulated and real-life studies of shift work indicate that caffeine reduces sleepiness and is useful as countermeasure for performance deteriorations during nighttime work. In combination with a nap, caffeine might be even more effective in contributing to a safer environment by maintaining performance and wakefulness at satisfying levels.

Sleep Deprivation

Sleep Characteristics

The ability to remain awake over a long period of time is of vital importance under specific conditions, such as military operations in times of crisis, medical care, and driving. Caffeine is used to stay awake during these periods. However, any intervention that significantly increases sleep loss affects sleep quality and sleep structure of subsequent sleep periods. The question is whether caffeine influences the relation between sleep deprivation and the quality and quantity of successive sleep.

Wesensten and colleagues (55) showed that a dose of 600 mg caffeine increased sleep onset latency after a sleep deprivation period of 64 h. However, no effects were found during a 12-h recovery sleep period commenced 20 h after caffeine administration which fits to the half-life of caffeine which is on average 3–5 h. Philip et al. (53) examined sleep latencies during recovery sleep 2–3 h after the consumption of 200 mg caffeine and after overnight sleep deprivation. They found that sleep latency was only delayed marginally (<1 min) compared with the placebo condition. Sleep efficiency was not influenced by caffeine in their study.

The effects of 200 mg caffeine on sleep latency following one night of sleep deprivation, in six volunteers without a history of regular coffee consumption were examined by Salín-Pascual and colleagues (56). They found no effects of caffeine on daytime sleepiness; similar sleep latencies were found in both the caffeine and the placebo conditions. Thus, even in subjects not accustomed to coffee, effects of caffeine were small or absent.

Another phenomenon challenging the circadian timing system is jet lag, the transient period of impairment following rapid travel to a different time zone. On arrival in the new time zone, the sleep–wake cycle is not timed appropriately relative to the time of day in the new situation. Jet lag is characterized by sleep disturbances, daytime sleepiness, and impaired performance (57). Beaumont and colleagues (58) studied the effects of caffeine on sleep and sleepiness after a seven-time zone eastward transmeridian travel. This double-blind, randomized, placebo-controlled study was performed on 27 healthy volunteers (aged between 19 and 47 years). In the caffeine condition, reduced levels of daytime sleepiness were observed. However, a dose of 300 mg SRC a day affected sleep quality on six subsequent recovery days (sleep latency increased, with less rebound of slow-wave sleep).

In conclusion, caffeine in simulated and real-life work situations is effective in counteracting fatigue and sleepiness, thereby improving performance, while the effects on sleep quality are modest.

Performance

A shortage of 1.3–1.5 h sleep for 1 night might result in a one-third reduction of daytime alertness. The hypothesis is that caffeine may help to maintain alertness at satisfying levels in situations where the sleep–wake cycle is disturbed, because the stimulating effects of caffeine have found to be especially salient under sub-optimal conditions, such as mental fatigue (59, 60).

Frontal brain regions are in particular sensitive to the effects of sleep loss. Metabolic activity, for example, reduced significantly in these regions during sleep deprivation (61). Cognitive processes mediated by the frontal cortex might therefore be particularly vulnerable to the detrimental effects of sleep loss. Especially, the prefrontal cortex is crucial in dynamically controlling and co-ordinating the activities of other, often widely separated, brain regions supporting more basic functions. Bonnet and Arand (52) showed that individuals who took a prophylactic nap and used caffeine during work shifts significantly increased performance on complex tasks such as logical reasoning and additions. A follow-up study (62), comparing the effects of repeated versus single-dose administration of caffeine and naps of 0, 2, 4, and 8 h taken before sleep loss confirmed the finding that alertness and performance during sleep loss improved by a combination of short naps and small repetitive doses of caffeine (150 mg caffeine) administered every 6 h starting at 1:30 a.m. on the first night of sleep loss. A repeated dose of 150 mg caffeine improved alertness and performance better than larger doses (300 and 400 mg) of caffeine. However, neither naps nor caffeine alone or combined could preserve functioning at baseline levels beyond 24 h after which alertness and functioning approached placebo levels.

Differential effects of moderate doses of caffeine (100, 200, or 300 mg) or placebo given after 72 h sleep deprivation formed the subject of Lieberman's study (63). Sixty-eight US Navy Sea–Air-Level trainees were tested after sleep deprivation on cognition and mood. Sleep deprivation and stress elicited in the simulated combat situation adversely affected performance and mood. However, 300 mg caffeine, but especially the 200-mg dose, improved visual vigilance, reaction time, and alertness. More complex performance, requiring fine motor control, was not affected by caffeine.

Gottselig and colleagues (64) studied the effects of 200 mg caffeine on cognitive control functions in healthy young men. In two periods, occurring 1 week apart, participants received either caffeine or placebo, after either 11 or 23 h of the 40-h sleep-deprivation period, according to a randomized, double-blind crossover design. A random number generation task was completed at 3-h intervals during the experimental session. It appeared that caffeine preserved simple aspects of cognitive performance during sleep deprivation, but did not so on more complex cognitive functions. Kohler and co-workers (65), on the other hand, did report an effect of 200 mg caffeine administered at midnight before an overnight sleep-deprivation period, on higher-level cognitive performance. The 14 young adults (aged between 18 and 36 years) showed faster reactions in a grammatical reasoning task after caffeine as compared with placebo.

Effects of 600 mg caffeine on alertness and psychomotor performance in 48 healthy men (aged between 19 and 38 years; ±6–8 cups of coffee) were evaluated by Wesensten and colleagues (55). Caffeine given after 64 h sleep deprivation improved alertness and psychomotor performance. Caffeine enhanced some aspects of higher order cognitive functions (complex judgement and conceptual efficiency), as well. A 600-mg dose was also used by Killgore et al. (66) in 29 men and 24 women on the ability to appreciate humour in visual (cartoons) or verbal (headlines) stimuli. Appreciating humour is generally regarded as one of the most complex forms of high-level cognition in humans. As expected, sleep loss for 49.5 h adversely affected the capacity to appreciate humour. However, there was no effect of caffeine on the appreciation of visual or verbal humour, although caffeine did improve simple psychomotor response speed and ratings of subjective sleepiness.

The effect of 200 mg caffeine on driving performance after partial sleep deprivation was examined in 16 students (mean age 23 years) (67). They either slept 5 h or were sleep deprived for the whole night until they had a 2-h drive (6–8 a.m.) on a dull, monotonous road. Caffeine clearly improved driving performance with fewer incidents and less subjective sleepiness. In a flight simulation task, the effects of 200 mg caffeine were examined during sustained wakefulness in 24 male students (aged between 25 and 31 years) (68). The observed positive effects of caffeine were in agreement with the effect on cognitive performance reported by Reyner and Horne (67).

Wesensten et al. (69, 70) studied the efficacy of 600 mg caffeine in maintaining performance and alertness during the early morning hours, when the combined effects of prolonged sleep loss and the circadian morning trough of alertness are most manifest. Ten healthy young adults were totally sleep deprived for 54.5 h. After they were awake for 41.5 h, they received double-blind 600-mg caffeine. Again, performance and alertness were significantly improved by using caffeine.

The former studies show that caffeine compensates for performance deteriorations induced by sleep deprivation. Simple task performance benefits most from caffeine.

Comments

Typically, caffeine studies use acute caffeine challenges following a period of abstinence (usually overnight). Some regular caffeine consumers experience a "withdrawal syndrome," starting on average after 12–24 h of abstinence with a peak between 20 and 48 h, which manifests itself in headaches, irritability, and occasionally nausea (71). This withdrawal syndrome may already start after a relatively short-term exposure from 6 to 15 days with doses above 600 mg caffeine a day. An important issue is whether the effects of caffeine, and individual differences in these effects in particular, can be explained by the relief of withdrawal effects (e.g., 72, 73), by the stimulating effects of caffeine itself or by both.

Rogers and colleagues (74) compared the effects of caffeine (1.2 mg/kg) in sleep-restricted (5 h) participants, who were either caffeine-withdrawn for 3 weeks to avoid acute withdrawal symptoms or received regular coffee or tea followed by overnight caffeine-withdrawal. The results supported the withdrawal reversal hypothesis: cognitive performance was affected negatively by overnight, acute caffeine withdrawal. Even after partial sleep deprivation and without withdrawal effects, cognitive performance was not improved by caffeine. James and Gregg (75) examined the effects of caffeine in healthy habitual coffee drinkers (aged between 17 and 52 years). The 1.75-mg/kg caffeine dose showed no significant mood-enhancing effects when participants were well rested and also did not produce restorative effects when mood was worsened by lack of sleep. All participants in this study were habitual caffeine consumers, although with strongly varying intake (180–680 mg per day). Interpretation of these results should be done with care because Attwood et al. (76) showed that high consumers (>200 mg/day) were more likely to report positive effects of caffeine than low consumers who in general did not report an effect of caffeine. High consumers may be more sensitive to the effects of caffeine, which may in turn drive their regular self-administration of caffeine. Expectancies on effects of caffeine could be involved, as well (77). Johnson and co-workers found that nocturnal sleep was associated with objectively measured daytime sleepiness but not with subjective sleepiness. Apparently, the subject's expectancy on the efficacy of caffeine determines his perception of wakefulness and alertness and may explain discrepancies in findings. It illustrates that baseline differences between high and low caffeine consumers might hinder explaining experimental results.

Hewlett and Smith (78) compared the effects of caffeine (1 mg/kg) on mood and performance in overnight withdrawn consumers and non-consumers (who by definition are not withdrawn). It should be noted that overnight caffeine withdrawal is part of most people's daily life. There was no evidence of negative effects of caffeine withdrawal on performance and mood. On the contrary, caffeine significantly improved performance, although there were differences between regular consumers and non-consumers. Caffeine tended to reduce reaction time in regular consumers whereas the opposite was true for non-consumers. Habitual users and non-users of caffeine were also studied by Haskell and colleagues (79), using a placebo-controlled, double-blind, balanced crossover design. They found in both groups, following overnight caffeine withdrawal, significant improvements in performance after 75 and 150 mg of caffeine. Concerning mood, caffeine tended to have greater benefits for mood of habitual users than for the non-consumers. The authors argued, in line with Attwood et al. (76), that basic differences between habitual consumers and non-consumers might explain why some individuals become caffeine consumers and others do not and why some people may profit more from caffeine than others.

Issues that need to be addressed by future research:

- Assess the influence of situational factors related to caffeine intake in the effects of caffeine.
- Retain detailed information total habitual caffeine intake from all sources.
- Measure the effects of caffeine as used everyday practice in non-withdrawn subjects.
- Determine the metabolic rate of caffeine while taking into account level and pattern of caffeine consumption, and co-current use of other recreational substances as nicotine and alcohol.
- Study over the day the changes in expectancy and motives why caffeine is taken.
- Look for strategies people use in their caffeine consumption to maintain wakefulness and alertness in suboptimal conditions like in shift work and/or during sleep deprivation.
- Unravel inter-individual differences in caffeine effects.
- Examine dose-dependent effects of caffeine on performance and well-being both in optimal and suboptimal states.
- Examine the different sensitivity to caffeine of different underlying brain structures.

References

1. Bruce M, Scott N, Lader M, Marks V. The psychopharmacological and electrophysiological effects of single doses of caffeine in healthy human subjects. *British Journal of Clinical Pharmacology* 1986;22:81–87.
2. Gevins A, Smith ME, McEvoy LK. Tracking the cognitive pharmacodynamics of psychoactive substances with combinations of behavioral and neurophysiological measures. *Neuropsychopharmacology* 2002;26:27–39.
3. Lieberman HR. The effects of ginseng, ephedrine, and caffeine on cognitive performance, mood and energy. *Nutrition Reviews* 2001;59:91–102.
4. Smith A, Sutherland D, Christopher G. Effects of repeated doses of caffeine on mood and performance of alert and fatigued volunteers. *Journal of Psychopharmacology* 2005;19: 620–626.
5. Yu G, Maskray V, Jackson SH, Swift CG, Tiplady B. A comparison of the central nervous system effects of caffeine and theophylline in elderly subjects. *British Journal of Clinical Pharmacology* 1991;32:341–345.
6. Zwyghuizen-Doorenbos A, Roehrs TA, Lipschutz L, Timms V, Roth T. Effects of caffeine on alertness. *Psychopharmacology* 1990;100:36–39.
7. Garattini S. *Caffeine*, *Coffee and Health*. New York: Raven Press; 1993.
8. Gupta BS, Gupta U. *Caffeine and Behaviour: Current Views and Research Trends*. Boca Raton, Florida: CRC Press LCC; 1999.
9. Nehlig A. *Coffee*, *Tea*, *Chocolate*, *and the Brain*. Boca Raton, Florida: CRC Press LCC; 2004.
10. Snel J, Lorist MM. *Nicotine*, *Caffeine and Social Drinking: Behaviour and Brain Function*. The Netherlands: Harwood Academic Publishers; 1998.
11. Arnaud MJ. Pharmacokinetics and metabolism of caffeine. In: Snel J, Lorist MM, editors. *Nicotine*, *Caffeine and Social Drinking: Behaviour and brain function*. The Netherlands: Harwood Academic Publishers; 1998: p. 153–165.
12. Fredholm BB, Bättig K, Holmén J, Nehlig A, Zvartau EE. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacological Reviews* 1999;51:83–133.
13. Satel S. Is caffeine addictive? - A review of the literature. *American Journal of Drug and Alcohol Abuse* 2006;32:493–502.
14. Daly JW. Mechanisms of action of caffeine. In: Garattini S, editor. *Caffeine*, *Coffee and Health*. New York: Raven Press; 1993: p. 97–150.
15. Daly JW, Fredholm BB. In: Nehlig A, editor. *Coffee*, *Tea*, *Chocolate*, *and the Brain*. Boca Raton, Florida: CRC Press LCC; 2004. p. 1–11.
16. Kalinchuk AV, Urrila AS, Alanko L, Heiskanen S, Wigren HK, Suomela M, Stenberg D, Porkka-Heiskanen T. Local energy depletion in the basal forebrain increases sleep. *The European Journal of Neuroscience* 2003;17:863–869.
17. Porkka-Heiskanen T, Strecker RE, Thakkar M, Bjorkum AA. Adenosine: A mediator of the sleep-inducing effects of prolonged wakefulness. *Science* 1997;276:1265–1267.
18. Huang ZL, Qu WM, Eguchi N, Chen JF, Schwarzschild MA, Fredholm BB, et al. Adenosine A_{2A}, but not A_1, receptors mediate the arousal effect of caffeine. *Nature Neuroscience* 2005;8:858–859.
19. Bättig K. Coffee, cardiovascular and behavioral effects current research trends. *Reviews on Environmental Health* 1991;9: 53–84.
20. Brice CF, Smith AP. Factors associated with caffeine consumption. *International Journal of Food Sciences and Nutrition* 2002;53:55–64.

21. Shohet KL, Landrum RE. Caffeine consumption questionnaire: a standardized measure for caffeine consumption in undergraduate students. *Psychological Reports* 2001;89:521–526.
22. Lane JD. Neuroendocrine responses to caffeine in the work environment. *Psychosomatic Medicine* 1994;56:267–270.
23. Mitler MM, Carskadon MA, Czeisler CA, Dement WC, Dinges DF, Graeber RC. Catastrophes, sleep, and public-policy - Consensus Report. *Sleep* 1988;11:100–109.
24. Garbarino S, Nobili L, Beelke M, De Carli F, Ferrillo F. The contributing role of sleepiness in highway vehicle accidents. *Sleep* 2001;24:203–6.
25. Smith AP. Effects of caffeine on attention: Low levels of arousal. In: Snel J, Lorist MM, editors. *Nicotine*, *Caffeine and Social Drinking: Behaviour and Brain Function*. The Netherlands: Harwood Academic Publishers; 1998: p. 215–227.
26. Hayashi M, Masuda A, Hori T. The alerting effects of caffeine, bright light and face washing after a short daytime nap. *Clinical Neurophysiology* 2003;114:2268–2278.
27. Snel J. Coffee and caffeine: sleep and wakefulness. In: Garattini S, editor. *Caffeine*, *Coffee and Health*. New York: Raven Press; 1993. p. 255–290.
28. Drapeau C, Hamel-Hébert I, Robillard R, Selmaoui B, Filipini D, Carrier J. Challenging sleep in aging: The effects of 200 mg of caffeine during the evening in young and middle-aged moderate caffeine consumers. *Journal of Sleep Research* 2006;15: 133–141.
29. Alford C, Bhatti J, Leigh T, Jamieson A. Caffeine-induced sleep disruption: Effects on waking the following day and its reversal with an hypnotic. *Human Psychopharmacology: Clinical and Experimental* 1996;11:185–198.
30. Åkerstedt T, Ficca G. Alertness-enhancing drugs as a countermeasure to fatigue in irregular work hours. *Chronobiology International* 1997;14:145–158.
31. Orbeta RL, Overpeck MD, Ramcharran D, Kogan MD, Ledsky R. High caffeine intake in adolescents: Associations with difficulty sleeping and feeling tired in the morning. *Journal of Adolescent Health* 2006;38:451–453.
32. Bernstein GA, Carroll ME, Thuras PD, Cosgrove KP, Roth ME. Caffeine dependence in teenagers. *Drug and Alcohol Dependence* 2002;66:1–6.
33. NAH. Caffeine: the inside scoop - the good, the bad, and the myth. Nutrition Action Health Letter 1996. Available from: www.cspinet.org/nah/good bad.htm
34. Anderson C, Horne JA. A high sugar content, low caffeine drink does not alleviate sleepiness but may worsen it. *Human Psychopharmacology: Clinical and Experimental* 2006;21: 299–303.
35. Basner RC. Shift-work sleep disorder–the glass is more than half empty. *The New England Journal of Medicine* 2005;353: 519–521.
36. Torsvall L, Akerstedt T, Gillander K, Knutsson A. Sleep on the night shift: 24-hour EEG monitoring of spontaneous sleep/wake behavior. *Psychophysiology* 1989;26:352–358.
37. Gillooly PB, Smolensky MH, Albright DL, Hsi B, Thorne DR. Circadian variation in human performance evaluated by the Walter Reed performance assessment battery. *Chronobiology International* 1990;7:143–153.
38. Folkard S, Tucker P. Shift work, safety and productivity. *Occupational Medicine* 2003;53:95–101.
39. Connor J, Norton R, Ameratunga S, Robinson E, Civil I, Dunn R, et al. Driver sleepiness and risk of serious injury to car occupants: population based case control study. *British Medical Journal* 2002;324:1125.
40. Personick M, Mushinski M. Highway fatalities: leading cause of work-related deaths. *Statistical Bulletin* (Metropolitan Life Insurance Company: 1984) 1997;78:19–25.
41. Wright KP, Jr., Myers BL, Plenzler SC, Drake CL, Badia P. Acute effects of bright light and caffeine on nighttime melatonin and temperature levels in women taking and not taking oral contraceptives. *Brain Research* 2000;873:310–317.
42. Wright KP, Jr., Badia P, Myers BL, Plenzler SC. Combination of bright light and caffeine as a countermeasure for impaired alertness and performance during extended sleep deprivation. *Journal of Sleep Research* 1997;6:26–35.
43. Wright KP, Jr., Badia P, Myers BL, Plenzler SC, Hakel M. Caffeine and light effects on night time melatonin and temperature levels in sleep-deprived humans. *Brain Research* 1997;747:78–84.
44. Shilo L, Sabbah H, Hadari R, Kovatz S, Weinberg U, Dolev S, et al. The effects of coffee consumption on sleep and melatonin secretion. *Sleep Medicine* 2002;3:271–273.
45. Babkoff H, French J, Whitmore J, Sutherlin R. Single-dose bright light and/or caffeine effect on nocturnal performance. *Aviation Space and Environmental Medicine* 2002;73:341–350.
46. Macchi MM, Bruce JN. Human pineal physiology and functional significance of melatonin. *Frontiers in Neuroendocrinology* 2004;25:177–195.
47. Landolt HP, Dijk DJ, Gaus SE, Borbély AA. Caffeine reduces low-frequency delta activity in the human sleep EEG. *Neuropsychopharmacology* 1995;12:229–238.
48. Landolt HP, Werth E, Borbély AA, Dijk DJ. Caffeine intake (200 mg) in the morning affects human sleep and EEG power spectra at night. *Brain Research* 1995;675:67–74.
49. Landolt HP, Rétey JV, Tönz K, Gottselig JM, Khatami R, Buckelmüller I, Achermann P. Caffeine attenuates waking and sleep electroencephalographic markers of sleep homeostasis in humans. *Neuropsychopharmacology* 2004;29: 1933–1939.
50. Wyatt JK, Cajochen C, Cecco AR-D, Czeisler CA, Dijk DJ. Low-dose repeated caffeine administration for circadian-phase-dependent performance degradation during extended wakefulness. *Sleep* 2004;27:374–381.
51. Rosa RR. Napping at home and alertness on the job in rotating shift workers. *Sleep* 1993;16:727–735.
52. Bonnet MH, Arand DL. Impact of naps and caffeine on extended nocturnal performance. *Physiology and Behavior* 1994;56: 103–109.
53. Philip P, Taillard J, Moore N, Delord S, Valtat C, Sagaspe P, Bioulac B. The effects of coffee and napping on nighttime highway driving: a randomized trial. *Annals of Internal Medicine* 2006;144:785–791.
54. Schweitzer PK, Randazzo AC, Stone K, Erman M, Walsh JK. Laboratory and field studies of naps and caffeine as practical countermeasures for sleep-wake problems associated with night work. *Sleep* 2006;29:39–50.
55. Wesensten NJ, Killgore WDS, Balkin TJ. Performance and alertness effects of caffeine, dextroamphetamine, and modafinil during sleep deprivation. *Journal of Sleep Research* 2005;14(3):255–266.
56. Salín-Pascual RJ, Valencia-Flores M, Campos RM, Castaño A, Shiromani PJ. Caffeine challenge in insomniac patients after total sleep deprivation. *Sleep Medicine* 2006;7:141–145.

57. Reilly T, Waterhouse J, Edwards B. Jet lag and air travel: Implications for performance. *Clinics in Sports Medicine* 2005;24: 367–380.
58. Beaumont M, Batéjat D, Piérard C, Van BP, Denis JB, Coste O, Doireau P, Chauffard F, French J, Lagarde D. Caffeine or melatonin effects on sleep and sleepiness after rapid eastward transmeridian travel. *Journal of Applied Physiology* 2004;96:50–58.
59. Weiss B, Laties VG. Enhancement of human performance by caffeine and the amphetamines. *Pharmacological Review* 1962;14:1–36.
60. Lorist MM, Snel J, Kok A. Influence of caffeine on information processing stages in well rested and fatigued subjects. *Psychopharmacology* 1994;113:411–421.
61. Thomas M, Sing H, Belenky G, Holcomb H, Mayberg H, Dannals R, et al. Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. *Journal of Sleep Research* 2000;9:335–352.
62. Bonnet MH, Gomez S, Wirth O, Arand DL. The use of caffeine versus prophylactic naps in sustained performance. *Sleep* 1995;18:97–104.
63. Lieberman HR, Tharion WJ, Shukitt-Hale B, Speckman KL, Tulley R. Effects of caffeine, sleep loss, and stress on cognitive performance and mood during U. S. Navy SEAL training. *Psychopharmacology* 2002;164:250–261.
64. Gottselig JM, Adam M, Rétey JV, Katami R, Achermann P, Landolt HP. Random number generation during sleep deprivation: Effects of caffeine on response maintenance and stereotypy. *Journal of Sleep Research* 2006;15:31–40.
65. Kohler M, Pavy A, Van den Heuvel C. The effects of chewing versus caffeine on alertness, cognitive performance and cardiac autonomic activity during sleep deprivation. *Journal of Sleep Research* 2006;15:358–368.
66. Killgore WDS, McBride SA, Killgore DB, Balkin TJ. The effects of caffeine, dextroamphetamine, and modafinil on humor appreciation during sleep deprivation. *Sleep* 2006;29: 841–847.
67. Reyner LA, Horne JA. Early morning driver sleepiness: Effectiveness of 200 mg caffeine. *Psychophysiology* 2000;37: 251–256.
68. Dagan Y, Doljansky JT. Cognitive performance during sustained wakefulness: a low dose of caffeine is equally effective as modafinil in alleviating the nocturnal decline. *Chronobiology International* 2006;23:973–983.
69. Wesensten NJ, Belenky G, Kautz MA, Thorne DR, Reichardt RM, Balkin TJ. Maintaining alertness and performance during sleep deprivation: Modafinil versus caffeine. *Psychopharmacology* 2002;159:238–247.
70. Wesensten NJ, Belenky G, Thorne DR, Kautz MA, Balkin TJ. Modafinil vs. caffeine: Effects on fatigue during sleep deprivation. *Aviation Space and Environmental Medicine* 2004;75: 520–525.
71. Dews PB. Caffeine: behavioral effects of withdrawal and related issues. *Food and Chemical Toxicology* 2002;40:1257–1261.
72. James JE. Does caffeine enhance or merely restore degraded psychomotor performance. *Neuropsychobiology* 1994;30: 124–125.
73. Rogers PJ, Dernoncourt C. Regular caffeine consumption: A balance of adverse and beneficial effects for mood and psychomotor performance. *Pharmacology Biochemistry and Behavior* 1998;59:1039–1045.
74. Rogers PJ, Heatherley SV, Hayward RC, Seers HE, Hill J, Kane M. Effects of caffeine and caffeine withdrawal on mood and cognitive performance degraded by sleep restriction. *Psychopharmacology* 2005;179:742–752.
75. James JE, Gregg ME. Effects of dietary caffeine on mood when rested and sleep restricted. *Human Psychopharmacology: Clinical and Experimental* 2004;19:333–41.
76. Attwood AS, Terry P, Higgs S. Exploring factors that mediate responsiveness to caffeine. *Appetite* 2006;47:258.
77. Johnson LC, Spinweber CL, Gomez SA. Benzodiazepines and caffeine: effect on daytime sleepiness, performance, and mood. *Psychopharmacology* 1990;101:160–167.
78. Hewlett P, Smith A. Acute effects of caffeine in volunteers with different patterns of regular consumption. *Human Psychopharmacology* 2006;21:167–180.
79. Haskell CF, Kennedy DO, Wesnes KA, Scholey AB. Cognitive and mood improvements of caffeine in habitual consumers and habitual non-consumers of caffeine. *Psychopharmacology* 2005;179:813–825.