CHAPTER 6

Effects of caffeine on sleep and cognition

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Abstract: Caffeine can be used effectively to manipulate our mental state. It is beneficial in restoring low levels of wakefulness and in counteracting degraded cognitive task performance due to sleep deprivation. However, caffeine may produce detrimental effects on subsequent sleep, resulting in daytime sleepiness. This justifies a careful consideration of risks related to sleep deprivation in combination with caffeine consumption, especially in adolescents. The efficacy of caffeine to restore detrimental effects of sleep deprivation seems to be partly due to caffeine expectancy and to placebo effects. The claim that stimulant effects of caffeine are related to withdrawal or withdrawal reversal seems to be untenable.

Keywords: caffeine; modafinil; staying awake; falling asleep; expectancy; withdrawal; recovery sleep; mental state.

Introduction

People are continuously engaged to find the optimum of their mental and physiological state. To reach that optimum, diverse strategies are used. In the case of preparing to go to bed, for example, people relax, lights are dimmed, and some people take a nightcap. When sleepy at times that one is expected to be alert and wakeful,

people might take a nap, go for a walk, or put on bright lights. However, for centuries, one of the most popular means to manipulate our physiological and mental state is the use of caffeine, mostly prepared as coffee. On one hand, it is deliberately used to counteract fatigue, to stay alert, perform at satisfying levels, and postpone sleep, while on the other hand, it is intentionally avoided by many to get a good night's sleep.

Caffeine is generally accepted to be a mild stimulant. It is affordable and easily available throughout the world and found in many products (see Table 1). After oral ingestion of caffeine, mostly in the form

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of coffee or tea, 99% of it is absorbed from the gastrointestinal tract into the bloodstream, peaking 30–60 min after ingestion. Faster absorption of caffeine is found for caffeine-containing chewing gum, with maximum levels reached between 45 and 80 min postadministration, while absorption rate for caffeine-containing capsules lies between 85 and 120 min (Kamimori et al., 2002). Caffeine diffuses throughout the entire body; it passes all biological membranes, including the blood–brain barrier and the placental barrier.

Most of the biological effects of caffeine, at levels reached during normal human consumption, are caused by way of antagonizing adenosine receptors, in particular, A1 and A2A receptors, and to a lesser degree, the A2B and A3 receptors. A1 and A2A adenosine receptors affect several mechanisms located in widespread areas of the brain, involved in the regulation of sleep, arousal, and cognition (Ribeiro and Sebastiao, 2010). Therefore, it is no surprise that caffeine, as an adenosine receptor antagonist, can modulate physiological and mental states (Table 2). This is supported by findings indicating that caffeine indeed attenuates the buildup of sleep propensity associated with wakefulness (Landolt, 2008b), although in rats, it was found (Wurts and Edgar, 2000) that caffeine did not block compensatory non-rapid eye movement (non-REM) sleep and sleep continuity. Moreover, it potently attenuates EEG markers of non-REM sleep homeostasis during sleep, as well as during wakefulness (Landolt, 2008b). Targeting the adenosine system by caffeine consumption therefore seems an effective tool to modulate individual vulnerability to the detrimental effects of sleep deprivation on cognitive performance, and sleep.

To be able to determine the effect of caffeine in people, individual differences have to be taken into account. Metabolic rate and the tolerance for effects of caffeine vary considerably from one person to the other. The half-life of caffeine is on average 3.7 h, ranging from 2 to 10 h, dependent on endogenous and exogenous factors. For example, metabolic speed of caffeine is increased by 30–50% in nicotine users, whereas a decrease is observed in pregnant women and woman taking oral contraceptives. Also there are large interindividual differences in sensitivity to caffeine due to genetic variations in the adenosine A2A receptor gene (Retey et al., 2007), the role adenosine and adenosine receptors play in non-REM sleep homeostasis, (Landolt, 2008b) and genotype-dependent differences in sleep (Landolt, 2008a). However, no systematic difference in the metabolism of caffeine is observed between men and women.

Besides the purposive use or avoidance of caffeine, it is frequently consumed unintentionally. People are not always aware that caffeine is added to many products to increase flavor and taste. The awareness (or unawareness) of caffeine consumption has important implications, not only for our well-being, but also for caffeine research.

Table 1. Caffeine contents of common products

Coffee, cup = 125 ml	Caffeine (mg)
Filtered, percolated	60–100
Drip	44
Instant	35–50
Pads, dark regular	90–95
Pads, mild	75–80
Cappuccino	60
Espresso cup = 50 ml	50–60
Decaffeinated coffee cup = 125 ml	2–4
Tea, cup = 125 ml	20–45
Soft drinks per 100 ml	
Cola's general	3–11
Cola' light	0–15
Ice tea	3–12
Energy drinks per 100 ml	30
Chocolate containing drinks per 100 ml	2–4
Chocolate/50 g	
Milk	2–25
Dark	8–60
Extra dark	30–210
Chocolate candy, bars, ice cream	2–10
Alcoholic drinks or shooters per 100 ml	50–120
Prescription and non-predescription medication	25–100

Source: Wendte et al. (2003).

Table 2. Central adenosine receptors affected by typical caffeine exposure

Receptor	Localization	Types of neurons	Effects of caffeine	Caffeine action
A1	Almost all brain areas, especially hippocampus, cerebral and cerebellar cortex, certain thalamic nuclei	All types of neurons (aspecific), especially linked to dopamine D_1 receptors	Antagonistic	Disinhibition of transmitter release
A2A	Dopamine-rich regions: striatum, nucleus accumbens, tuberculum olfactorium, hippocampus? cortex?	Colocalized with dopamine D_2 receptors	Antagonistic	Increase transmission via dopamine D_2 receptors

Source: Lorist and Tops (2003).

It is important to realize that estimating habitual caffeine intake is difficult and most likely results in lower estimates than actually consumed. Hence, the selection of participants based on their self-reported daily consumption of caffeine is often biased and unreliable. Careful screening of participants, who were selected on the basis of their habitual intake of 100–500 mg caffeine a day, by Wendte et al. (2003) revealed an actual caffeine consumption of 154–1285 mg (± 1.5–15 cups of coffee); quantities which were up to 250% higher than the self-reported values. In addition to the underreporting of consumed caffeine quantity, factors such as differences in brewing method, used coffee blend (Arabica coffee contains 2% of caffeine, Robusta coffee 4%), or serving size of caffeine-containing food hamper adequate estimation of caffeine intake.

In this chapter, effects of caffeine are described; in particular, effects on sleep–wake rhythmicity in sleep-deprived versus well-rested individuals.

Caffeine and sleep deprivation

A 24-h economy demands individuals to operate at times which are not "in sync" with their circadian clock. As a result, daily rhythms can become disrupted and, consequently, negatively affect our well-being. If the timing of sleep is not adapted to the circadian clock, this misalignment may result in a so-called circadian rhythm sleep disorder.

Disturbances of our circadian rhythmicity may cause disruptions in sleeping patterns and influence cognitive task performance, which can lead to suboptimal performance and even errors (Crochet et al., 2009; Ker et al., 2010). Jet lag and shift work are important factors that contribute to these deteriorations of performance and have indeed been found to be related to an increase in risk of injury (as discussed elsewhere in this volume). There is a strong need for interventions to guarantee that persons who run such risk can do their job safely and are able to restore disturbed circadian rhythms as soon and efficiently as possible. Different pharmacological aids are used to counteract work-related sleep problems and jet lag, and the question is whether caffeine might qualify as one of them (Coste and Lagarde, 2009). Evidence suggests that sleep-loss-induced deficits in alertness and vigilance can indeed be reversed or mitigated by stimulants such as caffeine (Lorist and Snel, 2008; Snel et al., 2004).

Sleep deprivation has been used in different studies to elucidate the role of caffeine in offsetting these effects. Benitez et al. (2009), for example, used a severe form of sleep deprivation in 14 males and 4 females (mean age 25.8 years, SD = 4.3), all mild or non-caffeine users (<300 mg/day). Participants had a normal 8-h night of sleep, followed by 77 h of continuous wakefulness. Placebo or caffeine (200 mg), in the form of two sticks of Alert gum, containing 100 mg of caffeine each, was assigned randomly at 1.00, 3.00, 5.00, and 7.00 a.m. during the

three subsequent nights. Performance was tested periodically over the 77-h period of continuous wakefulness, using the psychomotor vigilance test (PVT). The PVT is a simple visual reaction task, used to measure sustained attention. It measures the time it takes to respond to a visual stimulus. A biomathematical model was build to describe performance during the period of extended wakefulness. This model identified patterns in the data that suggested the presence of a performance inhibitor, called fatigue, that increased and saturated over the 77 h of continuous wakefulness. Caffeine was found to be able to inhibit the effects of fatigue. This result confirms the findings of former research (Balkin et al., 2004; Wesensten et al., 2002, 2004, 2005) with simple psychomotor tasks and tasks of executive functions, indicating that caffeine taken both incidentally or with the purpose of counteracting drowsiness in the morning, is effective in maintaining alertness and performance after prolonged periods of total sleep deprivation (i.e., 54.6–85 h).

The efficacy of caffeine in restoring cognitive processes like emotional perception, judgment, risk-taking, and planning after sleep deprivation was targeted in a series of double-blind studies by Killgore et al. (2009). They studied the effects of caffeine in 54 participants (age 18–36 years), who were sleep deprived for 45–50 h and subsequently tested. Before performing different cognitive tasks, they received one dose of 600 mg caffeine ($n=12$), 400 mg modafinil ($n=12$), 20 mg dextroamphetamine ($n=16$), or placebo ($n=14$). Like caffeine, modafinil promotes alertness and wakefulness. Modafinil is especially FDA approved to manage fatigue in narcolepsy and residual fatigue in sleep apnea and shift work sleep disorder (Rosenthal et al., 2008). Dextroamphetamine also has stimulant properties, known to promote wakefulness. It has been provided to pilots on long missions to help them remain focused and alert. However, dextroamphetamine can produce some side effects like palpitations, tachycardia, and elevated blood pressure (Caldwell and Caldwell, 2005). Modafinil has a disadvantage that it can be used only after informed consent. Participants in the Killgore et al. (2009) study were administered a test to measure the formation of abstract concepts 1 h after drug administration (i.e., after 45 h awake). Tests measuring planning time and cognitive processing started 3.5 h (i.e., 47.5 h awake) and 4.5 h after drug administration (i.e., after 48.5 h awake). The results of these studies showed that the three stimulants differentially affected the outcome of the three cognition tasks, suggesting that the stimulating effects of caffeine especially affected cognitive planning processes.

It seems clear that performance efficiency is affected by sleep deprivation and part of the performance deteriorations can indeed be counteracted by caffeine or other stimulants. However, it is important to realize that task performance not only relies on specific task demands and related cognitive abilities. The interaction between task, participant, and environment actually determines the quality of performance, especially during suboptimal situations. It is clear that some tasks are more challenging than others, and related changes in motivation might mask fatigue effects created by sleep deprivation.

Fatigue is a well-known and common phenomenon in sustained operations, such as long-distance driving and long-term continuous work (see Chapters 9 and 11 of this volume), in which a low information load does not promote motivation to perform. In many of such real-life situations, a sufficient level of motivation to work is required to perform adequately. Kilpelaiinen and colleagues studied the effect of caffeine and placebo on sustained attention and learning in such a vigilance situation. They also assessed subjective ratings of sleepiness, mood, motivation, and perceived task performance in their study (Kilpelaiinen et al., 2010). Fifteen military pilot students (age 23–24 years) took part in a series of tests in a flight simulator, in the 37 h sleep deprivation study. They received either placebo or 200 mg of caffeine twice a day (Kilpelaiinen et al., 2010). During the experiment, vigilance

was assessed six times (Mackworth clock test) and learning four times. The learning task consisted of learning the association between Japanese hiragana symbols and spoken syllables. Learning was tested 2 h later with five hiraganas from the previous learning session.

As expected, sleep deprivation decreased the amount of correct detections and increased reaction times in both the caffeine and placebo groups. The increase in number of false alarms was limited to the placebo group. Working memory, as tested in the learning task, remained unaffected during sleep deprivation. Kilpelaiinen et al. (2010) argued that the absence of performance decline in the learning task might partly be due to the stimulating nature of this task following a very exhausting and long-lasting vigilance task. With increasing sleep pressure, they observed that participants even wanted to perform the learning task during task breaks to help them stay awake, illustrating the importance of taking into account the environmental factors in sustained performance and sleep deprivation studies. Although a clear deterioration in vigilance performance was observed after sleep deprivation, subjective feelings of success remained stable across sustained wakefulness in the caffeine group. The feeling of success was measured with the phrase "How successful do you think you were in this task?" which was rated on a visual analog scale running from "not at all" to "very much." Similarly, Baranski (2007) in his study on confidence in judgment found that one night of sleep deprivation did not result in an impaired assessment of cognitive performance. It should be noted that the overconfidence in caffeine participants might have serious consequences in real-life work environments, like in aviation, because realistic self-perception is highly important in avoiding risks.

Caffeine and recovery sleep

There is little doubt among laymen and health professionals about the fundamental importance of sufficient, restorative sleep in maintaining one's physical and mental health. Maintaining a good sleep quality involves avoidance of substances that stimulate mind and body and disturb sleep habits. Caffeine, with its proven efficacy to counteract sleepiness, is one of the stimulants that may produce detrimental effects on subsequent sleep, especially when sleep is initiated at a time when the biological clock sends a strong waking signal as happens during daytime. This means a prudent use of caffeine. In other words, using caffeine at times that high mental alertness and physical activation hampers sleep quality should be avoided, in particular, in the hours shortly before going to sleep.

In people working shift hours, sleep habits have to be adapted to their irregular working schedule, which might cause specific problems in combination with caffeine consumption. Pecotic et al. (2008) evaluated sleep habits and explored whether these were influenced by caffeine consumption in 130 medical students, 68 physicians at the postgraduate study program, 162 specialists, and 93 nurses. Results indicated that the hours of sleep needed for feeling well rested depended on age, gender, work demands, and work schedule. However, respondents who consumed caffeine reported more trouble staying awake while listening to lectures or learning and while driving a car. Based on these results, the authors argued that caffeine consumption may impair sleep habits and quality of sleep, thereby hampering cognitive performance and wakefulness during nonsleep hours.

Whether caffeine use is consistently the cause of impaired sleep in everyday situation and not vice versa is questionable (Orbeta et al., 2006; Roehrs and Roth, 2008; Whalen et al., 2007). It was found that feeling tired in the morning induced high caffeine use which was associated with subsequent impaired sleep, indicating that cause and effect concerning the relation between caffeine and impaired sleep is not always clear. Another factor that may induce sleep disturbance in interaction with caffeine is vulnerability to stress (Drake et al., 2006). Drake and colleagues

showed that individuals with an objectively identified vulnerability to stress-induced sleep disturbance showed a stronger sleep-reactivity in response to a 3-mg/kg BW caffeine challenge than nonvulnerable individuals.

The effects of caffeine on daytime recovery sleep after 25 h of sleep deprivation were studied by Carrier et al. (2009). Young (age 20–30 years) and middle-aged volunteers (age 45–60 years) participated in a caffeine (200 mg) and placebo condition, spaced 1 month apart. Three hours before daytime recovery sleep, the participants took either the first 100 mg caffeine or placebo capsule, while the second 100 mg dose was taken 1 hour before daytime recovery sleep. An effect of caffeine on daytime recovery sleep was observed in both age groups, reflected in a decrease in sleep efficiency, sleep duration, slow-wave sleep, and REM sleep. Moreover, caffeine reduced non-REM sleep EEG synchronization during daytime recovery sleep. These results provide additional evidence that using caffeine to cope with night work and jet lag might result in detrimental effects on subsequent sleep.

However, no detrimental effects on recovery sleep were observed in the Philip et al. (2006) study. These authors examined nighttime driving performance between 2.00 and 3.30 a.m. after placebo, 30 min of napping, or 200 mg caffeine. An important difference between the Philip et al. (2006) study and studies in which a clear effect of caffeine on recovery sleep was observed might be the length of the sleep deprivation period used. Carrier et al. (2009), for example, exposed their participants to 25 h of sleep deprivation, while participants in the Philip et al. (2006) study were allowed to go to sleep immediately after the nighttime driving session (i.e., after 3.30 a.m.). Besides the duration of the sleep deprivation period, circadian rhythm might be another important factor that has to be taken into account in explaining differential effects of caffeine on recovery sleep. The participants in the Carrier et al. (2009) study were instructed to maintain a regular sleep–wake schedule before

the experimental session and the experimenters monitored these individuals during the 3 days before each experimental session to verify the absence of sleep deprivation. Effects of caffeine on sleep variables in individuals working night shifts or suffering from jet lag may be more pronounced because of stronger influences of circadian rhythms and related physiological processes in these individuals.

Effects of caffeine use on subsequent sleeping patterns have been related to its pharmacological actions. Although it is widely accepted that the predominant effect of caffeine is to block specific adenosinergic receptors, other mechanisms may play a role, as Ataka et al. (2008) presented in their study on candidate antifatigue substances on mental fatigue. Caffeine, used to increase alertness and wakefulness, might affect sleep by an effect on branched-chain amino acids. Branched-chain amino acids are used for the synthesis of proteins and are regarded as a biomarker of mental fatigue. Ataka et al. (2008) examined levels of these amino acids in 17 healthy participants who randomly received 100 mg/day caffeine or placebo twice a day for 8 consecutive days. Fatigue was induced by mental task performance (Uchida-Kraepelin psychodiagnostic test and advanced trail-making test). Task performance of the caffeine group was better than performance observed in the placebo group. However, subjective perception of fatigue, motivation, and sleepiness did not differ between both groups. These results are in line with the findings of Kilpelaiinen et al. (2010), suggesting that administration of caffeine improves task performance without decreasing the sensation of fatigue. An important observation of Ataka et al. (2008) was that plasma branched-chain amino acid levels in the caffeine group were lower than those observed in the placebo group, after the fatigue-inducing mental tasks, as well as after the recovery period (as a trend). These results indicate that caffeine can accelerate mental fatigue through increased activation of the brain, without an accompanying sensation of

increased fatigue. Bartley and Chute (1947) argued that mental fatigue might be regarded as a protection mechanism warning an individual that he or she needs a rest in order to prevent an overload of our cognitive system. Results of Ataka et al. (2008) imply that this warning mechanism, essential in reducing acute fatigue, is less effective after caffeine consumption. This might explain why caffeine used during daytime, particularly at later times of day, may have detrimental effects on subsequent sleep periods.

Caffeine and self-imposed sleep deprivation

Sleep disturbances have been associated with an increased risk of work absenteeism, decrements in vitality, social functioning, physical and mental health, and general quality of life (Lund et al., 2010). In young people, who tend to have irregular life styles and consequently do not get the sleep they need, sleep problems might give rise to academic problems. Caffeine can be used strategically to optimize the level of wakefulness, thereby improving daytime functioning in this group. It is important, though, to realize that nonjudicious use of caffeine may intensify their sleeping problems, since there is evidence for a greater physiological need for sleep in adolescents compared to other age groups. Lund et al. (2010) examined sleep quality in college students (age 17–24 years). Disturbed sleep was reported by 60% of the 1125 students, who completed a cross-sectional online survey about sleep habits. Students overwhelmingly stated that emotional stress and academic stress were important factors that negatively impacted sleep and explained 24% of the variance of the scores on the Pittsburgh Sleep Quality Index. It was noteworthy that caffeine consumption, consistency of sleep schedule, and daily hours of television and video game exposure were no significant predictors of sleep quality (Lund et al., 2010).

A different pattern of results was observed by Calamaro et al. (2009), who performed a study in middle and high school students (age 12–18 years) to examine the relation between technology use (e.g., watching television, text messaging, playing video games, surfing internet), caffeine intake, and quality of sleep. Calamaro et al. hypothesized that with increased technology use, especially late at night, more caffeine is consumed to stay awake. This behavior pattern, coupled with the early start times for middle schools and high schools that demand earlier weekday rise times, was expected to result in sleep deficits. The results showed that the hours spent with technology activities at night were indeed related to a decrease in sleep duration. Not surprisingly, the ability to stay alert and function adequately during the subsequent day was impaired by excessive daytime sleepiness in those students who got less sleep. In addition, caffeine consumption tended to be 76% higher in this group. Important implications of such a strategy concern the additional negative effects on nighttime sleep when trying to compensate daytime sleepiness by taking caffeine (Orbeta et al., 2006, Roehrs and Roth, 2008; Whalen et al., 2007). Altogether, these results warrant a careful consideration of risks related to sleep deprivation in combination with caffeine consumption, especially in middle and high school age groups.

Caffeine, sleepiness, and work quality

Caffeine promotes alertness during times of desired wakefulness in persons with jet lag or shift work disorder (for a review see Lorist and Snel, 2008). An important benefit of the effects of caffeine could be a reduced risk on injury and error during these periods. Tieges et al. (2004) showed that doses of 3 and 5 mg/kg body weight of caffeine in well-rested habitual caffeine consumers indeed reduced the number of errors compared to a placebo condition. Based on related changes in brain activity shown as enlarged error-related negativity, an event-related brain component that reflects anterior cingulate cortex activity, they

concluded that coffee consumption increased monitoring of ongoing cognitive processes for signs of erroneous outcomes.

The observed reduction in self-consciousness resulting in overconfidence after caffeine consumption (Kilpelaiinen et al., 2010) seems to contradict these findings, and might have consequences in real-life environments. Realistic self-perception is essential in avoiding risks. The important question whether under suboptimal conditions, for example, due to extended wakefulness, caffeine is still able to enhance the detection of erroneous responses and consequently minimize the risk of errors, was extensively studied in recent years (e.g., Lorist and Snel, 2008).

Ker et al. (2010) examined more specifically the role of caffeine in preventing errors or injuries caused by impaired alertness in individuals with jet lag or shift work. Their systematic review did not elucidate a relation between caffeine and injuries because none of the studies included measured injury outcomes. Concerning the occurrence of errors, Ker and colleagues observed that caffeine significantly reduced the number of errors compared to placebo.

One of the studies examined by Ker et al. (2010) was a study by Dagan and Doljansky (2006). These researchers evaluated the efficacy of caffeine (200 mg) and modafinil (200 mg) in maintaining cognitive performance after sleep deprivation in a flight simulation task. According to their results, both caffeine and modafinil significantly decreased the deviation from assigned altitude and velocity values compared to baseline levels during the nocturnal drop in cognitive performance, supporting that caffeine has a performance-increasing effect, especially under suboptimal conditions.

A second study reviewed by Ker et al. (2010) was performed by Philip et al. (2006). These authors measured nighttime highway driving performance of 12 young men immediately after 200 mg of caffeine, decaffeinated coffee (containing 15 mg of caffeine), and after napping in the car for 30 min. An increase was found in line crossings during nighttime driving compared with the daytime driving session. Lateral deviations have been found to be a frequent cause of sleep-related accidents. If daytime highway driving (between 6.00 p.m. and 7.30 p.m.) was used as a point of reference for nighttime driving (between 2.00 and 3.30 a.m.), no difference in driving performance was observed in 75% of the participants who consumed caffeine and 66% of them drove as well after a nap, indicating that drinking coffee or napping significantly reduced line crossing errors. These results illustrate the common practice that caffeine is used as an efficient countermeasure for sleep-related accidents which are known to occur most frequently in the middle of the night.

It is important to note that similar effects have also been found in well-rested individuals (Attwood et al., 2006; Childs and de Wit, 2006; Haskell et al., 2005; Hewlett and Smith, 2007). A common comment on caffeine's ability to improve performance is that little account is taken of the fact that caffeine withdrawal and withdrawal reversal might possibly obscure the net effects of caffeine. In a great deal of the experimental studies on the effects of caffeine, researchers have used the naturally occurring overnight caffeine abstinence period. In addition, participants are asked to abstain from their usual morning caffeine consumption prior to laboratory testing, and caffeine consumption is delayed until the experimental session. Improvements in performance following caffeine ingestion under these circumstances could reflect reversal of the adverse effects of the overnight caffeine withdrawal.

It is known that due to regular caffeine intake, the number of adenosine receptors in the central nervous system increases. As a result of this adaptive caffeine response, individuals become more sensitive to adenosine. A subsequent reduction of intake of caffeine as a blocker of adenosinergic receptors will increase the normal physiological effects of adenosine, resulting in withdrawal symptoms in tolerant caffeine users. Withdrawal symptoms, including headache, irritability, and an inability to concentrate, usually appear within

12–24 h after discontinuation of caffeine intake, peaking around 48 h (Juliano and Griffiths, 2004). These effects last from 1 to 5 days, representing the time required for the number of adenosine receptors in the brain to revert to "normal" levels, uninfluenced by caffeine consumption.

Keane and James (2008) examined the chronic effects of caffeine consumption in 15 healthy individuals (age 17–19 years). Participants alternated weekly between ingesting placebo and caffeine (1.75 mg/kg) three times daily for 4 consecutive weeks following either usual sleep or sleep restriction (40% of the usual amount). The effects of caffeine on brain activity, performance, and mood were examined after 6 days in which caffeine was consumed or after 6 days in which participants did not use caffeine-containing substances. The authors argued that the 6-day period warrants that the effects observed in the abstinence condition cannot be ascribed to withdrawal-related effects, since these effects last up to 5 days. Their results showed that the effects of caffeine on EEG activity were trivial and inconsistent, and no clear evidence was found of restorative effects of caffeine for performance and mood variables. They argued that caffeine is of no use to enhance human function or to reverse the negative effects of sleep loss. Other studies, however, did show increases in participants who were well-rested and not deprived of caffeine (e.g., Attwood et al., 2006; Childs and de Wit, 2006; Haskell et al., 2005; Hewlett and Smith, 2007). The lack of clear results in the Keane and James (2008) study might be related to the sleep restriction protocol they used. Keane and James did not observe changes in performance scores due to the sleep restrictions. In addition, no main effects were observed on EEG power, suggesting that the sleep restriction manipulation might have been too weak or the dependent measure too insensitive to caffeine effects to induce differential effects of caffeine between the usual sleep condition and the sleep restriction condition.

In order to avoid confounding of caffeine effects with tolerance or withdrawal, Michael et al. (2008) examined the effects of caffeine in 12 participants (age 18–29 years), who consumed either no caffeine or very little caffeine on a regular basis. The well-rested participants were tested on 2 separate days, using vigilance tests scheduled at baseline (around 9.00 a.m.) and at 30, 60, 120, 180, and 240 min after placebo or caffeine (200 mg) administration. During task performance, eye blink variables were measured to assess alertness.

In contrast with the outcome of the Keane and James (2008) study, the result of Michael et al. (2008) showed that, even though the participants were well rested, caffeine was able to reduce drowsiness, as deduced from ocular movements and reaction times, and these changes persisted for 3–4 h. The use of different ocular variables seemed to provide a sensitive measure to detect subtle changes in alertness induced by caffeine. Self-reports of sleepiness were not as sensitive; differences between the caffeine and placebo condition were only observed 30 min after substance administration. These findings support the conclusion that caffeine can have beneficial effects on performance and alertness (Michael et al., 2008), and that these effects do not seem to be related to withdrawal or withdrawal reversal since it is unlikely that tolerance has developed in the individuals who did not consume caffeine on a regular base.

The general conclusion, so far, seems clear; caffeine can be used effectively to manipulate mental state. It was found to be beneficial in restoring low levels of wakefulness and counteracting degraded task performance. However, caffeine may produce detrimental effects on subsequent sleep, resulting in daytime sleepiness.

Remaining issues

Expectancy

Caffeine is generally regarded as a stimulant, frequently used to make people feel more alert and ready to face daily challenges and to counteract

sleepiness. It is assumed that these properties are the main reason for consuming caffeine in a broad range of daily life situations and in research, as well. The stimulant effects of caffeine on physiological and mental states seem to profoundly be mediated by its pharmacological actions as an adenosine receptor antagonist. Van Dongen et al. (2001), for example, found in their participants, who were sleep deprived for 88 h and who received sustained low caffeine doses (0.3 mg/kg BW/h) during the last 66 h, that inertia was largely overcome by caffeine. They concluded that the caffeine-induced antagonism of adenosine receptors on the central nervous system results into an increase of unused adenosine in the brain upon awakening which might be the cause of sleep inertia.

However, expectations of caffeine (i.e., placebo) effects have been found to be an important additional factor to its psychostimulant effects. These expectations can trigger a series of physiological and psychological reactions, usually related to the pharmacological effects of caffeine consumption. Sun et al. (2007), for example, studied the effect of caffeine expectations on vigilance and cognitive task performance during 28 h of sleep deprivation. They informed 10 healthy male participants (age 18–20 years) that the capsules they had to ingest contained caffeine and gave them information about the stimulating effects of caffeine to increase the expectation of caffeine effects. Participants arrived at the laboratory at 6.00 a.m. and went through 28 successive hours of total sleep deprivation. Cognitive tests (letter cancelation task, continuous addition test) were administered every 2 h from 12.00 to 10.00 a.m. of the second day. Sun et al. (2007) found that an initial dose of 200 mg caffeine, administered at 12.00 a.m., followed 4 h later by a placebo helped to maintain cognitive performance during the period without sleep to a similar extent as the condition in which a double dose of caffeine was given. The placebo effect extended the cognitive boost without incurring the rise in blood pressure and heart rate that sometimes go together with caffeine consumption. This result suggests that this caffeine-plus-placebo regimen could be used when work schedules demand extended periods of alertness without sleep to maximize attention but minimize negative side effects.

Caffeine expectations were also examined in 16 young healthy volunteers (age 18–25 years) by Anderson and Horne (2008). In their study, participants performed a three-times 30-min PVT (separated by a 2-min break after every 30 min) after they had a light lunch; during this period, an early afternoon "dip" is usually experienced. Sleepiness was further enhanced by requiring participants to limit their prior night's sleep to 5 h. Participants were tested twice, either after they consumed a cup of decaffeinated coffee which was accompanied by verbal information that the coffee was decaffeinated (control) or after they consumed decaffeinated coffee after the experimenter informed them about the highly alerting effects of the "super" type coffee they were going to receive (expectancy). Significantly, fewer lapses and shorter reaction times were observed in the expectancy condition than after the control condition during the first hour of task performance, indicating that expectancy about consuming caffeine was effective in improving performance or preventing performance decrement in moderately sleepy people. It is surprising that while caffeine can take 30–40 min to become pharmacologically effective, the effects of expectancy seemed more rapid.

Anderson and Horne (2008) argued that the effects of caffeine expectations might be related to classical conditioning, that is, the expectancy effect is a conditioned response. Moreover, this effect might have been enhanced by knowledge of the effects of caffeinated beverages. Support for a role of classical conditioning in caffeine expectancy was provided by Attwood et al. (2008). They examined whether the effects of caffeine could be conditioned to the context of administration in 16 volunteers (age 18–26 years). Four conditioning trials were followed by a test session, in which participants received placebo before performing a simple reaction time task. Attwood et al. observed that

in the test session, the group who received 250 mg caffeine during the conditioning trials performed significantly faster during the test session than the group who had received placebo, indicating the development of a conditioned response. Possible involvement of expectancy effects in this study was reduced by presenting caffeine in a novel drink, and by not informing the participants about the contents of the beverage, making the finding all the more salient.

Caffeine expectancy effects are not limited to cognitive task performance but may be also present in physical task performance. Pollo et al. (2008) observed across participants who thought they consumed caffeine, that mean muscle work which was not accompanied by a decrease of perceived muscle fatigue, was regarded as evidence that caffeine expectancy could indeed counteract the symptoms of physical fatigue.

In sum, the effects elicited after administration of a placebo instead of caffeine illustrate that the efficacy of caffeine to restore detrimental effects of sleep deprivation on performance is partly due to caffeine expectancy.

Conclusions

Caffeine, a well-known antagonist of adenosinergic receptors, can be used effectively to modulate our mental state. Caffeine is found to be beneficial in restoring low levels of wakefulness and to counteract deteriorations in task performance related to sleep deprivation. However, the results also indicate that caffeine may produce detrimental effects on subsequent sleep, resulting in daytime sleepiness. The efficacy of caffeine to restore mental performance decline in suboptimal conditions seems to be partly due to caffeine expectancy. No support was found for the claim that stimulant effects of caffeine are related to withdrawal or withdrawal reversal. In conclusion, caffeine provides an adequate and common way to strategically adjust mental state, provided the effects on recovery sleep are taken into consideration.

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