Available online at www.sciencedirect.com
SCIENCE DIRECT®
Brain and Cognition 53 (2003) 82–94
Brain and Cognition
www.elsevier.com/locate/b&c

Caffeine, fatigue, and cognition

Monicque M. Lorist[a,b,*] and Mattie Tops[a,c]

[a] Experimental and Work Psychology, University of Groningen, Groningen, The Netherlands
[b] Department of Medical Physiology, University of Groningen, Groningen, The Netherlands
[c] Department of Psychiatry, University of Groningen, Groningen, The Netherlands

Accepted 21 July 2003

Abstract

Effects of caffeine and fatigue are discussed with special attention to adenosine–dopamine interactions. Effects of caffeine on human cognition are diverse. Behavioural measurements indicate a general improvement in the efficiency of information processing after caffeine, while the EEG data support the general belief that caffeine acts as a stimulant. Studies using ERP measures indicate that caffeine has an effect on attention, which is independent of specific stimulus characteristics. Behavioural effects on response related processes turned out to be mainly related to more peripheral motor processes. Recent insights in adenosine and dopamine physiology and functionality and their relationships with fatigue point to a possible modulation by caffeine of mechanisms involved in the regulation of behavioural energy expenditure.

Keywords: Caffeine; Fatigue; Reaction time; EEG; ERP; Adenosine; Dopamine; Arousal

1. Introduction

Coffee is a beverage known all over the world, and millions of humans drink it everyday. A significant proportion of the effects of coffee is related to the actions of caffeine, the best-known pharmacologically active constituent of coffee. The reasons for humans to consume caffeine are manifold. The common belief is that it affects the energetic state of subjects. There is indeed a considerable amount of research illustrating that the use of caffeine does result in increases of subjective energy and alertness (Bruce, Scott, Lader, & Marks, 1986; Gevins, Smith, & McEvoy, 2002; Lieberman, 2001; Yu, Maskray, Jackson, Swift, & Tiplady, 1991; Zwyghuizen-Doorenbos, Roehrs, Lipschutz, Timms, & Roth, 1990). In addition to these stimulant effects of coffee, it is a pleasurable experience to consume a cup of coffee for most people, and caffeine intake, either acute or chronic, appears to have only minor negative consequences on health.

Almost all caffeine comes from dietary sources (e.g., coffee, tea, and cocoa beverages). An important source of caffeine for children includes chocolate bars and soft drinks. Most of the coffee is consumed at home, while the second preferred place of consumption is at work. Especially at these work places, coffee is considered a pleasant occasion to break working hours (D'Amicis & Viani, 1993).

Caffeine use is self-limiting; subjects do not gradually increase the amount of caffeine normally used. In addition, the intake of a high dose of caffeine is not reinforced by positive and pleasant behavioural effects. The addictive potential of caffeine has been questioned frequently in the past. In a recent study Nehlig and Boyet (2000) found that in rats the functional activation of the shell of the nucleus accumbens, an area involved in addiction and reward, was only induced by the highest dose of caffeine (10 mg/kg). These findings showed that the usual human consumption level of caffeine fails to activate reward circuits in the brain, and therefore provide evidence that caffeine has only very low addictive potential.

In the present paper evidence is discussed regarding the effects of caffeine on human behaviour. Since caffeine

* Corresponding author. Fax: +31-50-363-6304.
E-mail address: m.m.lorist@ppsw.rug.nl (M.M. Lorist).

0278-2626/$ - see front matter © 2003 Elsevier Inc. All rights reserved.
doi:10.1016/S0278-2626(03)00206-9

is associated with enhanced cognition and some aspects of cognition are closely linked to specific neurotransmitter systems, we will review the effects of caffeine and try to correlate these data with known effects on neuromodulator systems. Behavioural, EEG, and ERP indices of performance will be examined.

2. Pharmacology of caffeine

After oral ingestion, caffeine is rapidly and almost completely (99%) absorbed from the gastrointestinal tract into the bloodstream (Arnaud, 1993; Fredholm, Bättig, Holmén, Nehlig, & Zvartau, 1999). Peak plasma concentrations are reached in about 30–60 min after consumption. Caffeine is widely distributed throughout the body, and it passes through all biological membranes, including the blood–brain barrier and the placental barrier. The elimination of caffeine occurs primarily by metabolism in the liver. Less than 5% is recovered unchanged in urine. The half-life of caffeine is approximately 3–5 h, although individual clearance rates vary considerably. For example, the clearance rate is speeded up with 30–50% by nicotine, while it is doubled in woman taking oral contraceptives.

3. Mechanisms underlying the central effects of caffeine

Caffeine, at doses comparable to those of typical human exposure, are primarily related to its actions to block adenosine receptors (Daly, 1993; Fredholm et al., 1999; Phillis, 1991). The ability of caffeine to block adenosine effects on these receptors can be observed already at low concentrations achieved after a single cup of coffee. Other mechanisms of action (e.g., inhibition of phosphodiesterase, mobilisation of intracellular calcium) demand higher concentrations of caffeine, unlikely to be reached by normal use of caffeine containing dietary sources.

Pharmacological studies indicate that the CNS effects of caffeine are mediated particularly by its antagonistic actions at the A_1 and A_{2A} subtypes of the adenosine receptors (Table 1). Adenosine A_1 receptors are present in almost all brain areas. The highest levels are found in the hippocampus, cerebral and cerebellar cortex, and certain thalamic nuclei (Fastbom, Pazos, & Palacios, 1987; Goodman & Snyder, 1982), while only moderate levels are found in caudate-putamen and nucleus accumbens. The presence of presynaptic adenosine A_1 receptors mediating inhibition of transmitter release has been demonstrated on virtually all types of neurons. There is considerable evidence for a link between adenosine A_1 receptors and dopamine D_1 receptors (see Ferré, Fredholm, Morelli, Popoli, & Fuxe, 1997). Adenosine A_{2A} receptors are found to be concentrated in the dopamine-rich regions of the brain. There is little evidence for A_{2A} receptors located outside striatum, nucleus accumbens, and tuberculum olfactorium, although functional data clearly suggests the presence of A_{2A} receptors in hippocampus and cortex. In the dorsal striatum, core and shell regions of the nucleus accumbens and the tuberculum olfactorium A_{2A} and dopamine D_2 receptors were found to be co-localized.

Svenningsson, Nomikos, and Fredholm (1999) have argued that blockade of A_{2A} receptors in striatopallidal neurons is crucial for the stimulatory action of caffeine. In addition, there is ample evidence that an intact dopaminergic neurotransmission is necessary for caffeine to be stimulatory (Ferré, Fuxe, Von Euler, Johansson, & Fredholm, 1992). Moreover, it has been shown that the effects of a low dose of caffeine can be mimicked by a selective adenosine A_{2A} receptor antagonist, but not by a selective adenosine A1 receptor antagonist (Svenningsson, Nomikos, Ongini, & Fredholm, 1997). Therefore, it seems justified to conclude that the interaction between caffeine in relevant doses and the dopaminergic transmission is based principally on enhancement of postsynaptic dopamine D_2 receptor transmission.

Dopamine is vital for the regulation of motor behaviour (e.g., co-ordinated motion) and for association learning linked to behavioural reinforcement. Moreover, a loss in striatal dopamine has been associated with a reduction in internally initiated control of behaviour; external cues seem to control behaviour instead of internal cues (Robbins, 1997). The antagonistic actions of caffeine at the A_{2A} adenosine receptors in the striatum

Table 1
Central adenosine receptors affected by typical human caffeine exposure

Receptor	Localization	Types of neurons	Effect of caffeine	Caffeine action
A_1	Almost all brain areas, especially hippocampus, cerebral and cerebellar cortex, certain thalamic nuclei	All types of neurons (aspecific) Especially linked to dopamine D1 receptors	Antagonistic	Disinhibition of transmitter release
A_{2A}	Dopamine rich regions: striatum, nucleus accumbens, tuberculum olfactorium, hippocampus? cortex?	Co-localized with dopamine D_2 receptors	Antagonistic	Increase transmission via dopamine D_2 receptors

are in accordance with the established reduction in risk of developing Parkinson's disease with increasing levels of caffeine consumption (Chen et al., 2001).

4. Behavioural effects of caffeine

The effects of caffeine on performance have been, and still are examined in many studies. More than 90 years ago, Hollingworth (1912) published the first placebo-controlled and double blind study, in which the effects of caffeine on human performance and sleep were examined. However, despite the large number of studies, it seems difficult to arrive at a coherent account of effects of caffeine on human performance.

In general, observations point to an inverted U-shaped dose–response curve for caffeine; lower doses have positive effects on performance, while doses above 500 mg cause a decrease in performance (e.g., Anderson & Revelle, 1983; Patat et al., 2000). Similarly, lower doses of caffeine are reliably associated with "positive" subjective effects, while higher doses of caffeine lead to a clear increase in measures of anxiety and tension (e.g., Loke, 1988; Thayer, 1989).

Human information processing consists of many cognitive operations ranging from the perception of information to the selection and subsequent execution of an action (e.g., button press). In addition, adequate and efficient performance relies on higher-level cognitive control processes, such as planning and preparation of activities. Although there is no strong agreement on the effects of caffeine on specific cognitive operations, there are indications that caffeine affects the attention system. Central to the idea of attention is that we can actively manipulate the impact that perceptual stimuli have on our information processing system (Kanwisher & Wojciulik, 2000). Attention can act as a multiplier of the neural response to relevant information, or can diminish the impact of irrelevant information. Thus, attention can be used to actively prepare or bias the human information processing system for the processing of specific stimulus features (Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999).

Using a paper and pencil version of a visual search task, Marsden and Leach (2000) showed an increase in performance efficiency with caffeine. After 250 mg black coffee without sugar, subjects detected more targets compared to a placebo condition. Ruijter, Lorist, Snel, and De Ruiter (2000c) used a computer version of a sustained attention task. They found, after a similar dose of caffeine, that subjects showed higher levels of perceptual sensitivity for relevant stimulus characteristics, as indicated by the signal detection parameter A'. In line with these findings, Kenemans and Lorist (1995) showed an increase in hit rate after caffeine treatment, while the number of false alarms did not change. They interpreted this improvement as evidence for an increase in the rate at which relevant information about the stimulus builds up in the processing system. These results indeed indicate that the information processing system seems more sensitive to relevant stimulus characteristics after caffeine.

On the other hand, Flaten and Elden (1999) examined the effects of caffeine on pre-pulse inhibition. Pre-pulse inhibition is supposed to index attentional pre-processing of a stimulus presented prior to a startle eye-blink reflex-eliciting stimulus. Their results showed that caffeine did not facilitate automatic attentional processes. Kenemans and Verbaten (1998) also illustrated the absence of an effect of caffeine on attention. They examined the effect of caffeine on various aspects of selective attention. A cueing task was used in which cues were presented either at the location of a subsequent target or at an alternative location, and a task was used in which relevant information was surrounded by irrelevant information. Their study showed that RTs were shorter after subjects had caffeine (1.5 and 3 mg/kg), however, these effects were not dependent upon attentional demands of specific task conditions. Therefore, they concluded that the effects of caffeine on behaviour were the result of improvements in preparation and/or execution of motor responses, rather than the result of an effect on the attention system.

Rees, Allen, and Lader (1999) found improvements in psychomotor performance in human subjects after a moderate dose of caffeine. These effects of caffeine on motor performance seem in accordance with the conclusion of Kenemans and Verbaten (1998). Moreover, the relationship between caffeine and motor behaviour has been supported in several investigations illustrating that caffeine reduced the time required to execute a response (e.g., Jacobson & Edgley, 1987; Smith, Tong, & Leigh, 1977). However, the effects of caffeine on motor performance are not always beneficial; negative or no effects are reported, as well (see Bättig, 1985; Fredholm et al., 1999; Van der Stelt & Snel, 1998).

The observed behavioural effects of caffeine are very diverse and, although not mentioned above, there are complicated interactions between stimulant actions of caffeine and the arousal level of subjects and the nature of task requirements. Even though sophisticated experimental paradigms can be used, and specific actions on cognitive functions can be defined with some confidence, behavioural measures do not seem to be sufficient to delineate precisely the specific actions of caffeine on the human information processing system (see also Gevins et al., 2002). An alternative approach to delineate the effects of caffeine on human information processing is to make use of more direct measures of brain activity.

5. EEG effects of caffeine

Caffeine is regarded as a mild stimulant acting on the central nervous system, producing diverse and complex effects, even when consumed in small quantities (Dews, 1984; Garattini, 1993). Behavioural indices of performance may not provide an accurate picture of these subtle and complex effects. Instead, measures of cortical brain activity, regarded as an index of cortical arousal (Rainnie, Grunze, McCarley, & Greene, 1994), might serve as a more sensitive indication of the stimulating effects of caffeine on brain functioning.

The electroencephalogram (EEG) shows more activation and changes towards faster frequency and lower-amplitude activity with increasing arousal. Already Gibbs and Maltby (1943) observed these effects after subjects were treated with caffeine. A robust finding observed in a number of studies concerns the reduction after caffeine treatment of power in the lower α or θ band (6–9 Hz; Bruce et al., 1986; Etevenon et al., 1989; Newman, Stein, Trettau, Coppola, & Uhde, 1992; Saletu, Anderer, Kinsperger, & Grünberger, 1987). Kenemans and Lorist (1995) found similar changes in brain-state indexed by the background EEG power spectrum. The most pronounced effect was found in the lower α range, while in the higher α and δ range the effect was smaller. In a study of Gevins et al. (2002), 200 mg caffeine did not elicit changes in resting EEG, however a reduction in α band power was observed during task performance. Contrary to these EEG effects, Gevins and colleagues failed to find effects of caffeine on behavioural measures. Patat et al. (2000) reported that caffeine (600 mg, slow release formulation) was able to counteract the effects of sleep deprivation (36 h) on the EEG, that is, caffeine increased the relative power in the α and β frequencies, while it decreased θ and δ power. Jones, Herning, Cadet, and Griffiths (2000) measured EEG for 3 min while subjects had their eyes closed in order to examine caffeine withdrawal effects. The effects illustrated that conform to the expectations caffeine withdrawal decreases alertness as reflected in increased EEG θ power. In sum, the EEG data indeed supports the stimulating effects of caffeine, although effects on specific cognitive activities cannot be distinguished, using this measure.

6. ERP effect of caffeine

Behavioural measures do not provide direct information about the effects of caffeine on brain function. These measures (e.g., RTs, errors) form the end product of many different cognitive operations (see Fig. 1). To delineate the specific effects of caffeine on the timing and organisation of cognitive processes occurring in the brain during task performance, event-related brain potentials (ERPs) are more convenient. ERPs are sequences of voltage deflections in the spontaneous electrical activity of the brain, which are time-locked to particular events such as the onset of a stimulus. They are revealed, by averaging brain activity recorded during many trials. ERPs can be recorded on trials in which stimuli are presented to which a response is or should be given, and stimuli that should be ignored, all within the same experimental task.

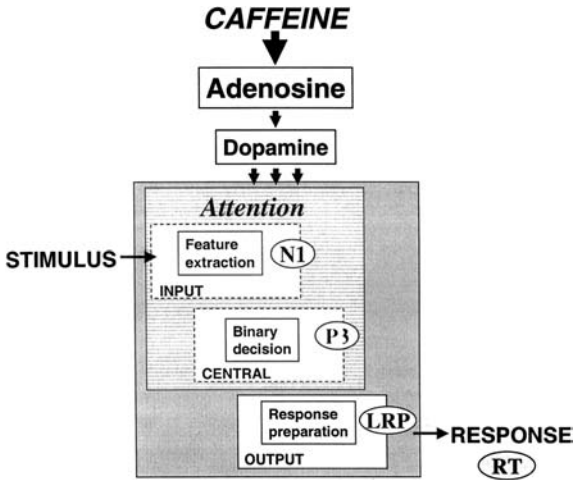

Fig. 1. A schematic representation of the actions of caffeine on the human information processing system. Physiological and behavioural indices thought to be related to different processes are depicted next to the concerning processes (LRP, lateralized readiness potential; RT, reaction time).

In Table 2 those studies, which sought to establish the effects of caffeine on the central nervous system, using ERP measures, are presented.

6.1. Attention

The behavioural effects of caffeine indicated that caffeine affects the attention system. Attention can modify neural activity in specific cortical areas, which are involved in the perceptual analysis of relevant stimulus information (e.g., Kanwisher & Wojciulik, 2000), that is, attention may enhance the responsivity of cells to specific stimulus features. Lorist et al. (1994a) studied feature-based attention by examining the effect of irrelevant information on the processing of relevant information. A task was used in which stimulus quality was manipulated, which is supposed to affect feature extraction processes (Sanders, 1983). The non-degraded stimuli consisted of a dot pattern surrounded by a rectangular frame of dots. In the degraded condition, dots were replaced from the frame into random position within the frame. The spatial arrangements of the dot patterns impaired the identification of the stimulus, as reflected in increased RTs and decreased accuracy. Caffeine had an effect on both the latency and amplitude

Table 2
Effects of caffeine treatment on the amplitude of ERP components

	N1	P2	N2b	P3	LRP	RT	Accuracy	Caffeine dose
Spilker and Callaway (1969)	—							300/500 mg (dependent on daily use)
Ashton, Millman, Telford, and Thompson (1974)	▲ (N1–P2)	CNV: ▲				▼		300 mg
Elkins et al. (1981)	—					▼		3/10 mg/kg BW
Wolpaw and Penry (1978)	▲ (Absence of decrease observed in placebo)	—						300 mg
Lorist, Snel, and Kok (1994a)	▲ Latency▼	▼		▲		▼	▲	200 + 50 mg
Lorist, Snel, Kok, and Mulder (1994b)	▲	▲	▲	▲		▼	—	200 + 50 mg
Kenemans and Lorist (1995)		Early positivity (Cz/Pz)		Latency▼	—	▼	▲	3 mg/kg BW
Lorist, Snel, Mulder, and Kok (1995)			▲	▼ Latency▼		▼ (No effects for high display load)	—	3 mg/kg BW
Lorist, Snel, Kok, and Mulder (1996)	▲	▼	▲	▲		▼	—	200 +50 mg
Lorist and Snel (1997)				▲	Onset▼	—	—	3 mg/kg BW
Ruijter, Lorist, and Snel (1999)	—	Fz: ▲		▲		▼	—	1, 3, and 7.5 mg/kg BW
Ruijter, De Ruiter, and Snel (2000a)		FPz: ▲	Att: ▲ Unatt ▼	▲ (Targets)		▼	—	250 mg
Ruijter, De Ruiter, Snel, and Lorist (2000b)	—	Fz: ▲	N2: ▲			—	▲ (Hits) ▲ (A′)	250 mg
Ruijter et al. (2000c)		Fz: ▲		▲		—	—	250 mg

▼, decrease; ▲, increase; –, no effect; and BW, body weight.

of the early exogenous N1 component. It was concluded that caffeine indeed increased the receptivity of subjects to external stimuli and moreover accelerates perceptual processing.

In a selective search task in which subjects had to search for a target letter on relevant spatial positions, a similar enhancement of the N1 was found (Lorist et al., 1994b; Lorist et al., 1995). However, this effect was consistent across stimulus conditions; it was not limited to relevant stimuli. Caffeine effects on the N1 component were not always present (Elkins et al., 1981; Kenemans & Lorist, 1995; Spilker & Callaway, 1969). Ruijter et al. (2000a, 2000b) neither observed an effect on the N1 component in a task in which subjects had to attend selectively to colour features nor in a task in which subjects had to attend selectively to spatially arranged bars of a specific size. They did report an enhancement of the exogenous frontal P2 component in the caffeine condition, which was interpreted as evidence supporting a more general increase in responsivity of caffeine to information, irrespective of stimulus relevance.

The effects of caffeine on selective visual attention were also examined in a study by Kenemans and Lorist (1995). Stimulus selection criteria in this study were spatial frequency and orientation. Kenemans and Lorist reported an increased positivity, specifically elicited by targets and frequency relevant stimuli, in the ERP in the 60–150 ms time interval after stimulus presentation. In this study subjects performed virtually perfect concerning the rejection of stimuli containing irrelevant spatial frequencies. Improvements in the caffeine condition therefore might be related to improvements in the analysis of orientation. The observed positivity might be a reflection of the orientation of stimuli, which have relevant frequency characteristics.

The ERP results seem to be in agreement with theories of visual attention. Effects on the N1 appear to be linked exclusively to spatial attention and are absent during attention to non-spatial stimulus features such as colour, size or spatial frequency (Hillyard, Mangun, Woldorff, & Luck, 1995). Attention to these non-spatial features is indexed by endogenous longer latency components (e.g., N2b, P3). In addition to the P2 effects mentioned earlier, Ruijter et al. (2000a) indeed reported effects of 250 mg caffeine on the N2b component, reflecting active orienting towards relevant stimulus features. The enlargement of the N2b component in response to relevant stimuli and the smaller N2b

component elicited by irrelevant stimuli could be interpreted as more active processing of relevant information, while irrelevant information was ignored more effectively. Lorist et al. (1994b, 1995, 1996) reported a similar increased N2b component, illustrating a more effective selection mechanism due to caffeine. These results support the idea that signal/noise ratios at the cortical levels are boosted due to caffeine.

Attention instructions can modify activity in specific brain areas related to the processing of relevant stimulus characteristics and thereby create a perceptual bias in order to prepare the system for the processing of relevant information (Kastner et al., 1999). If indeed caffeine has an effect on 'preparation' mechanisms, it might be hypothesised that the observed early, exogenous effects of caffeine are the result of more adequate preparation for upcoming information of the information processing system. These preparatory processes might appear as an increased negativity in the ERP elicited before a stimulus has been presented to the subject (Brunia, 1993). This negativity or contingent negative variation (CNV) is regarded as a measure of cortical responsiveness and is related to the degree of arousal of a subject. It should be noted that during this pre-stimulus period no behavioural indices of performance can be measured. Ashton et al. (1974) examined the effects of caffeine in an experiment, consisting of series of irregularly spaced flash–tone-response sequences. The interval between a flash and a tone was 1.25 s. During these intervals the CNV was recorded. The results of Ashton et al. showed that, as expected, caffeine increased the mean magnitude of the CNV 35–42 min after taking caffeine, which might be regarded as a sign of decreased thresholds resulting in a perceptual bias.

Considering the effects of caffeine on attention it can be carefully concluded that caffeine seems to have a general, positive effect. The information processing system seems to be modified to process relevant stimulus characteristics more effectively. However, before firm conclusions about the exact nature of the actions of caffeine on the attention system can be drawn more research is needed.

6.2. Arousal and fatigue

Another way of looking at the information processing system is to focus on arousal. It has been reported that the dependence of performance on cortical inputs changes with subjects' underlying arousal levels (Coull, Büchel, Friston, & Frith, 1999; Robbins, 1997; Sarter & Bruno, 2000; Turchi & Sarter, 1997). It has been argued that the most pronounced effects of caffeine would be expected in situations of lowered arousal or fatigue, or in tasks placing high demands on controlled processing, or conditions with explicit attentional demands (Bachrach, 1966; Lieberman, Spring, & Garfield, 1986; Weiss & Laties, 1962).

The results of Lorist et al. (1994a) indeed indicated that the effects of caffeine were more pronounced in the degraded stimulus condition, in which additional demands were placed on visual information processing by impairing the quality of stimuli. In a second task, used in the same study, Lorist and colleagues manipulated interstimulus interval to induce time uncertainty. In this task the results showed that the beneficial effects of caffeine were, as expected, larger in the task condition in which the targets were temporally unpredictable.

Hirvonen, Jääskeläinen, Näätänen, and Sillanaukee (2000) studied the effects of caffeine (100 mg), ethanol [0.55 g/kg in 10% (v/v) solution] and their combination on the mismatch negativity (MMN) in humans. The MMN provides a measure of the actual sensory information processed in the brain, generated by an automatic cerebral process that is necessary for conscious perception of differences between consecutive stimuli (Näätänen, 1992). The temporal and frontal neo-cortex are thought to be involved in MMN generation. Substances increasing cortical arousal enhance the MMN. This might lead to the expectation that caffeine affects the MMN. The results of Hirvonen and colleagues showed that given alone caffeine did not elicit effects on measured ERP components. This is in accordance with the results of Flaten and Elden (1999), who also found no effect of caffeine on automatic processes. However, under less optimal conditions, that is, in combination with ethanol caffeine antagonised the increase in MMN peak latency observed with ethanol.

In a study of Wolpaw and Penry (1978), in which subjects performed an auditory task, it was observed that after caffeine the 20% decrease in the N1–P2 amplitude observed in the placebo condition was absent. If indeed the effects elicited in the placebo condition are due to mental fatigue, these results provide additional evidence for the ability of caffeine to counteract effect of low arousal levels found in fatigued subjects.

Lorist et al. (1994b) compared more directly the effects of caffeine in a group of well-rested subjects with the effects in fatigued subjects. The influence of caffeine on early ERP components (N1 and N2b) was similar for well-rested and fatigued subjects. However, behaviour efficiency improved and the P3 component in fatigued subjects was larger after they consumed caffeine compared to the placebo condition. In the well-rested subjects, the caffeine and placebo conditions showed less pronounced differential effects. The results were interpreted as evidence that caffeine was able to counteract the effects of a low arousal state. In addition, the effects of caffeine on the P3b elicited by irrelevant target stimuli suggest that caffeine may alter the attitude toward the task at hand. Instead of sitting back and wait passively

for the next stimulus, subjects actively process information, although instructions told them that these stimuli were irrelevant (see Fig. 2).

This illustrates the complex nature of caffeine effects. It is clear that the effects of caffeine are not necessarily confined to conditions in which performance is degraded by factors such as fatigue or lack of interest. Beneficial effects can be demonstrated in subjects performing under more optimal conditions, as well (Nash, 1962; Weiss & Laties, 1962). However, the effects of caffeine seem to be found in particular when attentional control of perceptual functions is reduced.

Ruijter et al. (1999) used a complex dual-task paradigm to examine the effects of caffeine in high workload situations. If indeed caffeine can be regarded as an energy-increasing substance then, as was hypothesised by Ruijter and colleagues, caffeine might have beneficial effects in dual task performance. Using two choice reaction tasks, which subjects had to perform simultaneously, they found that the amplitude of the P3 component increased. The amplitude of the P3 was found to be related to resource demands available in the information processing system (Donchin, Kramer, & Wickens, 1986; Sirevaag, Kramer, Coles, & Donchin, 1984), and it reflects fluctuations in cortical arousal (Polich & Kok, 1995). Different doses were used by Ruijter, Lorist and Snel (1.0, 3.0, and 7.5 mg/kg BW), the 3.0 mg/kg BW showed the most positive going P3. This might be related to the U-shaped dose–response curve for caffeine. Again, the observed ERP effects were not reflected in behavioural indices of task performance, which illustrates nicely that although caffeine does not always seem to have clear effects on behaviour measures, the ERP results show more specific effects.

6.3. Response-related processing

Behavioural data indicated that caffeine has an effect on the motor system. To determine more precisely the effects of caffeine on response related processes, Lorist and Snel (1997) used a paradigm in which a target letter was flanked by compatible, incompatible, neutral or no information. The effect of caffeine on the lateralised readiness potential (LRP) was examined. The LRP is an ERP component supposed to reflect the time at which preparation of the overt response has begun at a central motor level. Lorist and Snel observed that caffeine had an effect on the onset latency of this component in those stimulus categories in which target letters were surrounded by irrelevant information. The caffeine effect was not present if a target letter appeared alone on the screen. Theories of attention state that there is a limitation on how much one can attend to at one time. Therefore, one has to select relevant information in the environment to attend to at appropriate times to perform optimally. Interference from simultaneously occurring information should be prevented from becoming conscious. The results of Lorist and Snel indicate that the distracting influence of irrelevant information was reduced in the caffeine condition and consequently,

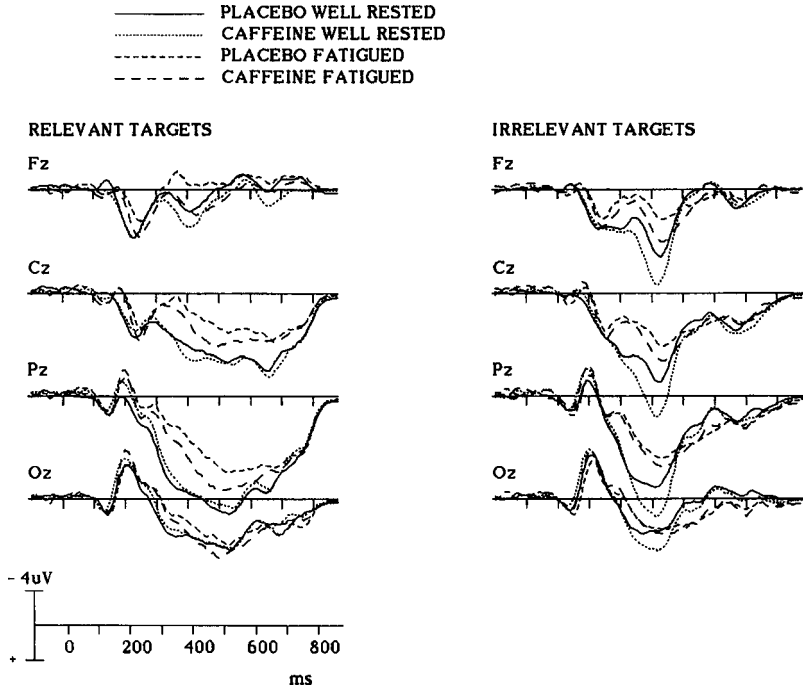

Fig. 2. Average stimulus-locked event-related potential (ERP) waveforms for well rested and fatigued subjects, evoked during the presentation of relevant (left) and irrelevant (right) information. ERPs are superimposed for the placebo and caffeine condition (modified from Lorist et al., 1994b).

information about the relevant target letter was available faster. As a result, this information could be passed earlier to the response system than in the placebo condition and an adequate reaction could be selected and executed.

Kenemans and Lorist (1995) did not find an effect of caffeine on the LRP. The decrease in RTs in combination with the unaffected LRP onsets suggests that caffeine might have an effect on processes taking place after response preparation, that is, on the output stages. This is in accordance with findings of Jacobson and Edgley (1987) and Smith et al. (1977) who observed an effect of caffeine on movement time. Although the number of studies is very limited, these observations do not seem to be in agreement with the supposed role of caffeine in response preparation. The effects of caffeine on the motor system, seems to be confined to effects on more peripheral mechanisms.

7. Caffeine and dopamine function

There is ample evidence from animal research that caffeine can increase behaviours related to dopamine (see Fredholm et al., 1999). As a result of the inhibition of adenosine A_{2A} receptors by caffeine, transmission via dopamine D_2 receptors is increased (Ferré et al., 1992), and consequently effects on behaviour related to dopamine are expected. The human data presently reviewed seem to be largely compatible with this dopaminergic framework. For instance, the generally observed inverted U-shaped dose–response curve for caffeine in humans is analogues to the dose–response curve for dopamine stimulation in the prefrontal cortex in animals observed by Arnsten and Goldman-Rakic (1998). They showed that there appears to be an optimal range and either too little or too much dopamine results in diminished prefrontal cortex functioning. Also interesting in this context are the findings of Gilbert, Dibb, Plath, and Hiyane (2000). Using an EEG α-power measure, they found that caffeine intake increased left frontal activation relative to right frontal activation. A relative dominance of left compared to right frontal activation has been linked to activity in the mesocorticolimbic dopaminergic system mediating approach motivation (Davidson, 1999). This dopaminergic system projects more densely to left than right frontal cortex.

In accordance with indications that caffeine affects the attention system, dopamine D_2 receptors have been demonstrated to modulate neural networks involved in both selective and involuntary attention (Kähkönen et al., 2001). Additionally, monoaminergic neurotransmitters were found to suppress spontaneous background activity while enhancing cortical neural responses to a stimulus, thereby focussing neural activity to brain structures specific for the processing of particular information (Mattay et al., 1996). Dopamine release in the nucleus accumbens and the onward effects through connections via the nucleus reticularis thalami is postulated to enhance sensory processing, especially in response to stimulus salience, and a sensorimotor gating function has been postulated for the nucleus accumbens and its output to perceptual as well as motor systems (Gray, Kumari, Lawrence, & Young, 1999).

Stimulatory effect of caffeine on motor behaviour is one of the most obvious effects observed in animal research. Garrett and Holtzman (1994) showed that dopamine receptor antagonists could block the stimulatory effects of caffeine on motor behaviour in rats, and the direct injection of an adenosine A_{2A} receptor agonist into the nucleus accumbens leads to a decreased locomotion (Barraco, Martens, Parizon, & Normile, 1993; Hauber & Münkle, 1997). Our review of human data, although limited, supports the role of caffeine on more peripheral motor processes.

The observed arousal enhancing effect of caffeine is also compatible with a dopaminergic mechanism. As mentioned earlier, Svenningsson et al. (1999) have argued that blockade of A_{2A} receptors is essential for the stimulatory action of caffeine. This hypothesis is in agreement with available evidence supporting that an intact dopaminergic neurotransmission is necessary for caffeine to be stimulatory (Ferré et al., 1992). As for direct links between ERP components and neurotransmitters, no exclusive relations have been determined in the literature. However, dopaminergic neurotransmission may play an important role in the generation of the P3. This was inferred from the sensitivity of this ERP component to dopamine-enhancing drugs in patients with Parkinson's disease (Stanzione et al., 1991). Also a relationship has been reported between the P3 and the dopamine D_2 receptor A1 allele (Hill et al., 1998; Noble, Berman, Ozkaragoz, & Ritchie, 1994).

Despite this compatibility between caffeine effects and the dopamine framework the data are not specific enough to preclude the involvement of other neuromodulator systems or interpretations. Especially acetylcholine has also received attention as a relevant target of action for caffeine (e.g., Porkka-Heiskanen, 1999). For example, Rainnie et al. (1994) examined the neural mediator(s) of the stimulating effects of caffeine on EEG arousal. They found that caffeine increased firing rates in mesopontine cholinergic neurons, which have been found to participate in the production of EEG arousal. These cholinergic neurons are inhibited by adenosine, providing a coupling mechanism linking EEG arousal and caffeine. These findings provide strong evidence for the role of caffeine in the behavioural state of arousal.

8. Dopamine and fatigue

The combination of recent insights in a predominantly dopaminergic mechanism of caffeine's influence in relevant doses (see Fredholm et al., 1999) and reported interactions between caffeine and fatigue is very interesting in the light of recent data and ideas about the role of dopaminergic systems in fatigue and energy expenditure.

Recently, central fatigue, common in several disorders like Parkinson's disease, chronic fatigue syndrome, atypical depression or multiple sclerosis, has been causally linked to hampered dopaminergic functioning in striato-thalamo-cortical fibres (Chaudhuri & Behan, 2000; Gold & Chrousos, 1998; Sudarsky, 1993). Additionally, decreased dopamine secretion, possibly secondary to damage to the basal ganglia, may underlie fatigue and impaired attention in polio survivors (Bruno & Zimmerman, 2000). Further support for the relation between dopaminergic functioning and central fatigue, is also provided by growing evidence, suggesting that lowered activity of the hypothalamic-pituitary-adrenocortical axis, causing low levels of cortisol, is a shared feature of diverse fatigue syndromes (Heim, Ehlert, & Hellhammer, 2000; Nicolson & Van Diest, 2000). Aspects of reward related dopaminergic activity in the nucleus accumbens is dependent on glucocorticoid modulation (e.g., Nakahara, Nakamura, Oki, & Ishida, 2000). The resulting hampered mesolimbic dopaminergic function may be causal to the symptoms of fatigue common to the hypocortisolismic syndroms (Gold & Chrousos, 1998).

Based on animal studies, nucleus accumbens dopamine also has been proposed to be central in every day (acute) fatigue, by regulating the propensity for expending energy or exerting effort (Neill & Justice, 1981; Salamone, Aberman, Sokolowski, & Cousins, 1999; Szechtman, Talangbayan, Ganaran, Dai, & Eilam, 1994). Especially dopamine D_2 receptor functioning was found to be related to effects concerning energy expenditure (Szechtman et al., 1994; Tataranni et al., 2001). Salamone suggested that release of dopamine in the nucleus accumbens might be an important part of the neural process that enables organisms to overcome work-related response costs. The nucleus accumbens may indirectly perform cost/benefit analyses, setting constraints on energy expenditure that profoundly influences the relative allocation of instrumental responses toward various alternatives, such that accumbens dopamine depletion biases behaviour in the direction of lower effort alternatives (Salamone et al., 1999). Additional evidence is provided by pharmacological studies, reporting that dopaminergic agents are able to increase energetic arousal (vigour; e.g., Corr & Kumari, 2000; Dalley et al., 2002).

Dopamine function may also be linked to individual differences in vigour and susceptibility to fatigue and effort sense. Depue and Collins (1999) reviewed evidence that argued for extraversion being considered the trait underlying dopamine functioning. Extraversion has been found to be inversely correlated with perceived physical exertion (Morgan, 1994) and fatigue (Watson, Wiese, Vaidya, & Tellegen, 1999), while it was positively correlated with preferred exercise intensity (Morgan, 1994) and vigour (e.g., Depue & Collins, 1999; Watson et al., 1999). Moreover, low scores on extraversion have been identified as a risk factor in the development of burnout (Bellani et al., 1996; Wagenvoort, VanYperen, Hoogduin, & Schaap, 1998).

9. Caffeine, adenosine, and fatigue

As reviewed above, caffeine interacts with fatigue to influence behaviour and related ERPs. In addition, there is ample evidence that lower doses of caffeine are reliably associated with "positive" subjective effects. After caffeine, subjects reported that they felt energetic, imaginative, efficient, self-confident, and alert; they felt able to concentrate and were motivated to work but also had the desire to socialize (see Fredholm et al., 1999). Additionally, the effects of caffeine on performance have been found to interact with extraversion and time of day (e.g., Revelle, Humphreys, Simon, & Gilliland, 1980). Moreover, some of the negative mood effects observed after prolonged sleep deprivation, are reduced by caffeine (Penetar et al., 1993).

Sleep propensity increases in the course of wakefulness and adenosine is a promising candidate for a fatigue or sleep-inducing factor. Its concentration is higher during wakefulness than during sleep, it accumulates in the brain during prolonged wakefulness, and local perfusions as well as systemic administration of adenosine and its agonists induces sleep and decreases wakefulness (see Porkka-Heiskanen, 1999). Adenosine also has been suggested to serve as a feedback signal to cells to decrease activity under increased metabolic demand, a function that would be well suited for a fatigue/sleep factor (Benington & Heller, 1995; Newby, 1984). Dopamine, in turn, has been thought to play only a minor role in sleep–wake regulation, yet compounds that block dopamine re-uptake or enhance dopamine release potently promote wakefulness. Based on animal research, Wisor et al. (2001) argued that adenosine–dopamine interactions might be involved in the effects of caffeine on sleep regulation.

It is known from research on acute mental fatigue that mental processes tend to slow down with the number of times in a row these processes are performed (i.e., time-on-task). Since adenosine concentrations increase during cell activity and thereby inhibit cell activity, it could be expected that it not only serves as a negative feedback inhibitor in response to time awake,

but in response to time-on-task and task-load, as well. Although this has not been studied yet, some research has been done on caffeine effects related to time-on-task. Van der Stelt and Snel (1998) concluded that caffeine regularly improves vigilance performance, although differences in task parameters seem to play an important role. As mentioned earlier, improvements due to caffeine treatment are noticed not only in fatigued subjects performing tasks in protracted sessions, but these effects may more easily become manifest under these circumstances (Koelenga, 1993).

10. General conclusions

The neurochemical mechanisms underlying the central effects of caffeine suggest that caffeine can influence a large number of cognitive functions, but may have a special relationship with fatigue, vigour and wakefulness. The effects of caffeine on human information processing are indeed diverse. As indicated by behavioural measurements, a general improvement in the efficiency of information processing is observed after caffeine, while the EEG data support the general belief that caffeine acts as a stimulant. The conclusions based on these measures about the specific effects of caffeine on human cognition, are not straightforward. The general idea is that caffeine affects information processing through an effect on the perceptual system and on output related processes. However, ERP measures are necessary to examine these hypotheses more precisely. Studies on the effects of caffeine on human information processing, using ERP measures are limited in number and therefore conclusions should be drawn with care. The ERP studies indicate that caffeine has an effect on attention, which is independent of specific stimulus characteristics. The behavioural effects on response related processes turned out to be mainly related to more peripheral motor processes.

A major problem in determining the effects of caffeine on human information processing is that although caffeine might have similar effects in different brain structures, the functional consequences of these effects may be quite different in different task paradigms and under different arousal states. Moreover, the link between the effects of caffeine on the information processing system and underlying neurochemical mechanisms is not clear-cut. Most research that studies the effects of neurochemicals on behaviour has been conducted in non-humans. Although a lot can be learned about humans by studying animals, these data cannot simply be extrapolated to humans. In this area certainly more research on human subjects is necessary.

Still, recently obtained new insights in adenosine and dopamine physiology and functionality and their relationships with fatigue, vigour and wakefulness provide an interesting opportunity for new research questions and theory regarding the effects of caffeine on human behaviour. The neurochemical mechanisms underlying the central effects of caffeine, the effects on human information processing, and the interactions of caffeine with fatigue, time of day and personality, all point to a possible modulation by caffeine in everyday doses of mechanisms involved in the regulation of behavioural energy expenditure.

Acknowledgments

This work has been supported by the Netherlands Organization for Scientific Research (NWO) as part of the Netherland concerted research action ''Fatigue at Work.''

References

Anderson, K. J., & Revelle, W. (1983). The interactive effects of caffeine, impulsivity and task demands on a visual search task. *Personality and Individual Differences, 4*, 127–134.

Arnaud, M. J. (1993). Metabolism of caffeine and other components of coffee. In S. Garattini (Ed.), *Caffeine, coffee and health* (pp. 43–95). New York: Raven Press.

Arnsten, A. F., & Goldman-Rakic, P. S. (1998). Noise stress impairs prefrontal cortical cognitive functioning in monkeys. Evidence for a hyperdopaminergic mechanism. *Archives of General Psychiatry, 55*, 362–368.

Ashton, H., Millman, J. E., Telford, R., & Thompson, J. W. (1974). The effect of caffeine, nitrazepam and cigarette smoking on the contingent negative variation in man. *Electroencephalography and Clinical Neurophysiology, 37*, 59–71.

Bachrach, H. (1966). Note on the psychological effects of caffeine. *Psychological Reports, 18*, 86.

Barraco, R. A., Martens, K. A., Parizon, M., & Normile, H. J. (1993). Adenosine A_{2A} receptors in the nucleus accumbens mediate locomotion depression. *Brain Research Bulletin, 31*, 397–404.

Bättig, K. (1985). The physiological effects of coffee consumption. In M. N. Clifford, & K. C. Willson (Eds.), *Coffee: Botany, biochemistry and production of beans and beverages* (pp. 394–439). London: Croom Helm.

Bellani, M. L., Furlani, F., Gnecchi, M., Pezzotta, P., Trotti, E. M., & Bellotti, G. G. (1996). Burnout and related factors among HIV/AIDS health care workers. *AIDS Care, 8*, 207–221.

Benington, J. H., & Heller, H. C. (1995). Restoration of brain energy metabolism as the function of sleep. *Progress in Neurobiology, 45*, 347–360.

Bruce, M., Scott, N., Lader, M., & Marks, V. (1986). The psychopharmacological and electrophysiological effects of single doses of caffeine in healthy human subjects. *British Journal of Clinical Pharmacology, 22*, 81–87.

Brunia, C. H. M. (1993). Waiting in readiness: Gating in attention and motor preparation. *Psychophysiology, 30*, 327–339.

Bruno, R. L., & Zimmerman, J. R. (2000). Word finding difficulty as a post-polio sequelae. *American Journal of Medical Rehabilitation, 79*, 343–348.

Chaudhuri, A., & Behan, P. O. (2000). Fatigue and basal ganglia. *Journal of Neurological Sciences, 179*, 34–42.

Chen, J. F., Xu, K., Petzer, J. P., Staal, R., Xu, Y. H., Beilstein, M., Sonsalla, P. K., Castagnoli, K., Castagnoli Jr., N., & Schwarzschild,

M. A. (2001). Neuroprotection by caffeine and A_{2A} adenosine receptor inactivation in a model of Parkinson's disease. *Journal of Neuroscience*, *21*, RC143, 1–6.

Corr, P. J., & Kumari, V. (2000). Individual differences in mood reactions to D-amphetamine: A test of three personality factors. *Journal of Psychopharmacology, 14*, 371–377.

Coull, J. T., Büchel, C., Friston, K. J., & Frith, C. D. (1999). Noradrenergically mediated plasticity in a human attentional neuronal network. *NeuroImage, 10*, 705–715.

Dalley, J. W., Chudasama, Y., Theobald, D. E., Pettifer, C. L., Fletcher, C. M., & Robbins, T. W. (2002). Nucleus accumbens dopamine and discriminated approach learning: Interactive effects of 6-hydroxydopamine lesions and systematic apomorphine administration. *Psychopharmacology*, DOI 10.1007/s00213-002-1078-2.

Daly, J. W. (1993). Mechanisms of action of caffeine. In S. Garattini (Ed.), *Caffeine, coffee and health* (pp. 97–150). New York: Raven Press.

D'Amicis, A., & Viani, R. (1993). The consumption of coffee. In S. Garattini (Ed.), *Caffeine, coffee and health* (pp. 1–16). New York: Raven Press.

Davidson, R. J. (1999). Neuropsychological perspectives on affective styles and their cognitive consequences. In T. Dalgleish, & M. J. Power (Eds.), *Handbook of cognition and emotion* (pp. 103–123). Toronto: Wiley.

Depue, R. A., & Collins, P. F. (1999). Neurobiology of the structure of personality: Dopamine, facilitation of incentive motivation, and extraversion. *Behavioral and Brain Sciences, 22*, 491–569.

Dews, P. B. (1984). *Caffeine: Perspectives from recent research*. Berlin: Springer.

Donchin, E., Kramer, A. F., & Wickens, C. (1986). Applications of brain event-related potentials to problems in engineering psychology. In M. G. H. Coles, E. Donchin, & S. W. Porges (Eds.), *Psychophysiology: Systems, processes, and applications* (pp. 702–718). New York: Guilford Press.

Elkins, R. N., Rapoport, J. L., Zahn, T. P., Buchsbaum, M. S., Weingartner, H., Kopin, I. J., Langer, D., & Johnson, C. (1981). Acute effects of caffeine in normal prepubertal boys. *American Journal of Psychiatry, 138*, 178–183.

Etevenon, P., Peron-Magnan, P., Guillou, S., Toussaint, M., Gueguen, B., Deniker, P., Loo, H., & Zarifian, E. (1989). A pharmacological model of local cerebral activation. EEG cartographyof caffeine effects in normals. In N. C. Andreasen (Ed.), *Brain imaging: Applications in psychiatry* (pp. 171–180). Washington: American Psychiatric Press.

Fastbom, J., Pazos, A., & Palacios, J. M. (1987). The distribution of adenosine A1 receptors and 5′-nucleotidase in the brain of some commonly used experimental animals. *Neuroscience, 22*, 813–826.

Ferré, S., Fredholm, B. B., Morelli, M., Popoli, P., & Fuxe, K. (1997). Adenosine–dopamine receptor–receptor interactions as an integrative mechanism in the basal ganglia. *Trends in Neurosciences, 20*, 482–487.

Ferré, S., Fuxe, K., Von Euler, G., Johansson, B., & Fredholm, B. B. (1992). Adenosine–dopamine interactions in the brain. *Neuroscience, 51*, 501–512.

Flaten, M. A., & Elden, Å (1999). Caffeine and prepulse inhibition of the acoustic startle reflex. *Psychopharmacology, 147*, 322–330.

Fredholm, B. B., Bättig, K., Holmén, J., Nehlig, A., & Zvartau, E. E. (1999). Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacological Reviews, 51*, 83–133.

Garattini, S. (1993). *Caffeine, coffee and health*. Raven Press: New York.

Garrett, B. E., & Holtzman, S. G. (1994). D_1 and D_2 dopamine receptor antagonists block caffeine-induced stimulation of locomotor activity in rats. *Pharmacology, Biochemistry and Behavior, 47*, 89–94.

Gevins, A., Smith, M. E., & McEvoy, L. K. (2002). Tracking the cognitive pharmacodynamics of psychoactive substances with combinations of behavioural and neurophysiological measures. *Neuropsychopharmacology, 26*, 27–39.

Gibbs, F. A., & Maltby, G. L. (1943). Effect on the electrical activity of the cortex of certain depressant and stimulant drugs—barbiturates, morphine, caffeine, benzedrine and adrenalin. *Journal of Pharmacology and Experimental Therapeutics, 78*, 1–10.

Gilbert, D. G., Dibb, W. D., Plath, L. C., & Hiyane, S. G. (2000). Effects of nicotine and caffeine, separately and in combination, on EEG topography, mood, heart rate, cortisol, and vigilance. *Psychophysiology, 37*, 583–595.

Gold, P. W., & Chrousos, G. P. (1998). The endocrinology of melancholic and atypical depression: Relationships to neurocircuitry and somatic consequences. *Proceedings of the Association of American Physicians, 111*, 22–34.

Goodman, R. R., & Snyder, S. H. (1982). Autoradiographic localization of adenosine receptors in rat brain using [^{3}H]cyclohexyladenosine. *The Journal of Neuroscience, 2*, 1230–1241.

Gray, J. A., Kumari, V., Lawrence, N., & Young, A. M. J. (1999). Functions of the dopaminergic innervations of the nucleus accumbens. *Psychobiology, 27*, 225–235.

Hauber, W., & Münkle, M. (1997). Motor depressant effects mediated by dopamine D_2 and adenosine A_{2A} receptors in the nucleus accumbens and the caudate-putamen. *European Journal of Pharmacology, 323*, 127–131.

Heim, C., Ehlert, U., & Hellhammer, D. H. (2000). The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. *Psychoneuroendocrinology, 25*, 1–35.

Hillyard, S. A., Mangun, G. R., Woldorff, M. G., & Luck, S. J. (1995). Neural systems mediating selective attention. In M. S. Gazzaniga (Ed.), *The cognitive neurosciences* (pp. 665–681). Cambridge: MIT Press.

Hill, S. Y., Locke, J., Zezza, N., Kaplan, B., Neiswanger, K., Steinhauer, S. R., Wipprecht, G., & Xu, J. (1998). Genetic association between reduced P300 amplitude and the DRD2 receptor A1 allele in children at high risk for alcoholism. *Biological Psychiatry, 43*, 40–51.

Hirvonen, J., Jääskeläinen, I. P., Näätänen, R., & Sillanaukee, P. (2000). Adenosine A_1/A_{2A} receptors mediate suppression of mismatch negativity by ethanol in humans. *Neuroscience Letters, 278*, 57–60.

Hollingworth, H. L. (1912). The influence on caffeine on mental and motor efficiency. *Archieves of Psychology, 22*, 1–166.

Jacobson, B. H., & Edgley, B. M. (1987). Effects of caffeine on simple reaction time and movement time. *Aviation, Space, and Environmental Medicine, 58*, 1153–1156.

Jones, H. E., Herning, R. I., Cadet, J. L., & Griffiths, R. R. (2000). Caffeine withdrawal increases cerebral blood flow velocity and alters quantitative electroencephalography (EEG) activity. *Psychopharmacology, 147*, 371–377.

Kähkönen, S., Ahveninen, J., Jääskeläinen, I. P., Kaakkola, S., Näätänen, R., Huttunen, J., & Pekkonen, E. (2001). Effects of haloperidol on selective attention. A combined whole-head MEG and high-resolution EEG study. *Neuropsychopharmacology, 25*, 498–504.

Kanwisher, N., & Wojciulik, E. (2000). Visual attention: insights from brain imaging. *Nature Neuroscience Reviews, 1*, 91–100.

Kastner, S., Pinsk, M., De Weerd, P., Desimone, R., & Ungerleider, L. (1999). Increased activity in human visual cortex during directed attention in the absence of visual stimulation. *Neuron, 22*, 751–761.

Kenemans, J. L., & Lorist, M. M. (1995). Caffeine and selective visual processing. *Pharmacology, Biochemistry and Behaviour, 52*, 461–472.

Kenemans, J. L., & Verbaten, M. N. (1998). Caffeine and visuo-spatial attention. *Psychopharmacology, 135*, 353–360.

Koelenga, H. S. (1993). Stimulant drugs and vigilance performance: A review. *Psychopharmacology, 111*, 1–16.

Lieberman, H. R. (2001). The effects of ginseng, ephedrine, and caffeine on cognitive performance, mood and energy. *Nutrition Reviews, 59*, 91–102.

Lieberman, H. R., Spring, B. J., & Garfield, G. S. (1986). The behavioral effects of food constituents: strategies used in studies of amino acids, protein, carbohydrate and caffeine. *Nutrition Reviews. Supplement, 44*, 61–70.

Loke, W. H. (1988). Effects of caffeine on mood and memory. *Physiology and Behavior, 44*, 367–372.

Lorist, M. M., Snel, J., & Kok, A. (1994a). Influence of caffeine on information processing stages in well rested and fatigued subjects. *Psychopharmacology, 113*, 411–421.

Lorist, M. M., Snel, J., Kok, A., & Mulder, G. (1994b). Influence of caffeine on selective attention in well-rested and fatigued subjects. *Psychophysiology, 31*, 525–534.

Lorist, M. M., Snel, J., Kok, A., & Mulder, G. (1996). Acute effects of caffeine on selective attention and visual search processes. *Psychophysiology, 33*, 354–361.

Lorist, M. M., Snel, J., Mulder, G., & Kok, A. (1995). Aging, caffeine, and information processing: an event-related potential analysis. *Electroencephalography and Clinical Neurophysiology, 96*, 453–467.

Lorist, M. M., & Snel, J. (1997). Caffeine effects on perceptual and motor processes. *Electroencephalography and Clinical Neurophysiology, 102*, 401–413.

Marsden, G., & Leach, J. (2000). Effects of alcohol and caffeine on maritime navigational skills. *Ergonomics, 43*, 17–26.

Mattay, V. S., Berman, K. F., Ostrem, J. L., Esposito, G., Van Horn, J. D., Bigelow, L. B., & Weinberger, D. R. (1996). Dextroamphetamine enhances "neural network-specific" physiological signals: a positron-emission tomography rCBF study. *The Journal of Neuroscience, 16*, 4816–4822.

Morgan, W. P. (1994). Psychological components of effort sense. *Medicine and Science in Sports and Exercise, 26*, 1071–1077.

Näätänen, R. (1992). *Attention and brain function*. London: Erlbaum.

Nakahara, D., Nakamura, M., Oki, Y., & Ishida, Y. (2000). Lack of glucocorticoids attenuates the self-stimulation-induced increase in the in vivo synthesis rate of dopamine but not serotonin in the rat nucleus accumbens. *European Journal of Neuroscience, 12*, 1495–1500.

Nash, H. (1962). *Alcohol and caffeine*. Springfield, IL: Thomas.

Nehlig, A., & Boyet, S. (2000). Dose–response study of caffeine effects on cerebral functional activity with a specific focus on dependence. *Brain Research, 858*, 71–77.

Neill, D. B., & Justice, J. B. (1981). An hypothesis for a behavioral function of dopaminergic transmission in nucleus accumbens. In R. B. Chronister, & J. F. DeFrance (Eds.), *The neurobiology of the nucleus accumbens* (pp. 343–350). Brunswick, ME: Haer Institute for Electrophysiological Research.

Newby, A. C. (1984). Adenosine and the concept of 'retaliatory metabolites'. *Trends in Biochemical Science, 9*, 42–44.

Newman, F., Stein, M. B., Trettau, J. R., Coppola, R., & Uhde, T. W. (1992). Quantitative electroencephalographic effects of caffeine in panic disorders. *Psychiatry Research: Neuroimaging, 45*, 105–113.

Nicolson, N. A., & van Diest, R. (2000). Salivary cortisol patterns in vital exhaustion. *Journal of Psychosomatic Research, 49*, 335–342.

Noble, E. P., Berman, S. M., Ozkaragoz, T. Z., & Ritchie, T. (1994). Prolonged P300 latency in children with the D_2 dopamine receptor A_1 allele. *American Journal of Human Genetics, 54*, 658–668.

Patat, A., Rosenzweig, P., Enslen, M., Trocherie, S., Miget, N., Bozon, M., Allain, H., & Gandon, J. (2000). Effects of a new slow release formulation of caffeine on EEG, psychomotor and cognitive functions in sleep-deprived subjects. *Human Psychopharmacology (Clin. Exp.), 15*, 153–170.

Penetar, D., McCann, U., Thorne, D., Kamimori, G., Galinski, C., Sing, H., Thomas, M., & Belenky, G. (1993). Caffeine reversal of sleep deprivation effects on alertness and mood. *Psychopharmacology, 112*, 359–365.

Phillis, J. W. (1991). *Adenosine and adenine nucleotides as regulators of cellular function*. Boca Raton, FL: CRC Press.

Polich, J., & Kok, A. (1995). Cognitive and biological determinants of P300: an integrative review. *Biological Psychology, 41*, 103–146.

Porkka-Heiskanen, T. (1999). Adenosine in sleep and wakefulness. *Annual Medicine, 31*, 125–129.

Rainnie, D. G., Grunze, H. C. R., McCarley, R. W., & Greene, R. W. (1994). Adenosine inhibition of mesopontine cholinergic neurons: Implications for EEG arousal. *Science, 263*, 689–692.

Rees, K., Allen, D., & Lader, M. (1999). The influences of age and caffeine on psychomotor and cognitive function. *Psychopharmacology, 145*, 181–188.

Revelle, W., Humphreys, M. S., Simon, L., & Gilliland, K. (1980). The interactive effect of personality, time of day, and caffeine: A test of the arousal model. *Journal of Experimental Psychology: General, 109*, 1–31.

Robbins, T. W. (1997). Arousal systems and attentional processes. *Biological Psychology, 45*, 57–71.

Ruijter, J., Lorist, M. M., & Snel, J. (1999). The influence of different doses of caffeine on visual task performance. *Journal of Psychophysiology, 13*, 37–48.

Ruijter, J., De Ruiter, M., & Snel, J. (2000a). The effects of caffeine on visual selective attention to color: An ERP study. *Psychophysiology, 37*, 427–439.

Ruijter, J., De Ruiter, M., Snel, J., & Lorist, M. M. (2000b). The influence of caffeine on spatial-selective attention: An ERP study. *Clinical Neurophysiology, 111*, 2223–2233.

Ruijter, J., Lorist, M. M., Snel, J., & De Ruiter, M. (2000c). The influence of caffeine on sustained attention: An ERP study. *Pharmacology, Biochemistry and Behaviour, 66*, 29–38.

Salamone, J. D., Aberman, J. E., Sokolowski, J. D., & Cousins, M. S. (1999). Nucleus accumbens dopamine and rate of responding: Neurochemical and behavioral studies. *Psychobiology, 27*, 236–247.

Saletu, B., Anderer, P., Kinsperger, K., & Grünberger, J. (1987). Topographic brain mapping of EEG in neuropsychopharmacology. Part II: Clinical applications (Pharmaco EEG Imaging). *Methods and Findings in Experimental and Clinical Pharmacology, 9*, 385–408.

Sanders, A. F. (1983). Towards a model of stress and human performance. *Acta Psychologica, 53*, 61–97.

Sarter, M., & Bruno, J. P. (2000). Cortical cholinergic inputs mediating arousal, attentional processing and dreaming: Differential afferent. *Neuroscience, 95*, 933–952.

Sirevaag, E. J., Kramer, A. F., Coles, M. G. H., & Donchin, E. (1984). P300 amplitude and resource allocation. *Psychophysiology, 21*, 598–599.

Smith, D. L., Tong, J. E., & Leigh, G. (1977). Combined effects of tobacco and caffeine on the components of choice reaction-time, heart rate, and hand steadiness. *Perceptual and Motor Skills, 45*, 635–639.

Spilker, B., & Callaway, E. (1969). Effects of drugs on "augmenting/reducing" in averaged visual evoked responses in man. *Psychopharmacologia, 15*, 116–124.

Stanzione, P., Fattapposta, F., Giunti, P., D'Alessio, C., Tagliati, M., Affricano, C., & Amabile, G. (1991). P300 variations in Parkinsonian patients before and during dopaminergic monotherapy: A suggested dopamine component in P300. *Electroencephalography and Clinical Neurophysiology, 80*, 446–453.

Sudarsky, L. (1993). Central mechanisms of fatigue. In D. M. Dawson, & T. D. Sabin (Eds.), *Chronic fatigue syndrome* (pp. 109–114). Boston: Little, Brown.

Svenningsson, P., Nomikos, G. G., & Fredholm, B. B. (1999). The stimulatory action and the development of tolerance to caffeine is associated with alterations in gene expression in specific brain regions. *Journal of Neuroscience, 19*, 4011–4022.

Svenningsson, P., Nomikos, G. G., Ongini, E., & Fredholm, B. B. (1997). Antagonism of adenosine A2A receptors underlies the behavioural activating effect of caffeine and is associated with reduced expression of messenger RNA for NGFI-A and NGFI-B in caudate-putamen and nucleus accumbens. *Neuroscience, 79*, 753–764.

Szechtman, H., Talangbayan, H., Ganaran, G., Dai, H., & Eilam, D. (1994). Dynamics of behavioral sensitization induced by the dopamine agonist quinpirole and a proposed central energy control mechanism. *Psychopharmacology, 115*, 95–104.

Tataranni, P. A., Baier, L., Jenkinson, C., Harper, I., Parigi Del, A., & Bogardus, C. (2001). A Ser311Cys mutation in the human dopamine receptor D2 gene is associated with reduced energy expenditure. *Diabetes, 50*, 901–904.

Thayer, R. E. (1989). *The biopsychology of mood and arousal*. New York: Oxford University Press.

Turchi, J., & Sarter, M. (1997). Cortical acetylcholine and processing capacity: Effects of cortical cholinergic deafferentation on crossmodal divided attention in rats. *Cognitive Brain Research, 6*, 147–158.

Van der Stelt, O., & Snel, J. (1998). Caffeine and human performance. In J. Snel, & M. M. Lorist (Eds.), *Nicotine, caffeine and social drinking: Behaviour and brain function* (pp. 167–183). The Netherlands: Harwood Academic Publishers.

Wagenvoort, M. A., VanYperen, N. W., Hoogduin, C. A. L., & Schaap, C. P. D. R. (1998). Persoonskenmerken en burnout: De medierende rol van coping-stijl. *Nederlands Tijdschrift voor de Psychologie, 53*, 128–143.

Watson, D., Wiese, D., Vaidya, J., & Tellegen, A. (1999). The two general activation systems of affect: Structural findings, evolutionary considerations, and psychobiological evidence. *Journal of Personality and Social Psychology, 76*, 820–838.

Weiss, B., & Laties, V. G. (1962). Enhancement of human performance by caffeine and the amphetamines. *Pharmacological Reviews, 14*, 1–36.

Wisor, J. P., Nishino, S., Sora, I., Uhl, G. H., Mignot, E., & Edgar, D. M. (2001). Dopaminergic role in stimulant-induced wakefulness. *The Journal of Neuroscience, 21*, 1787–1794.

Wolpaw, J. R., & Penry, J. K. (1978). Effects of ethanol, caffeine, and placebo on the auditory evoked response. *Electroencephalography and Clinical Neurophysiology, 44*, 568–574.

Yu, G., Maskray, V., Jackson, S. H. D., Swift, C. G., & Tiplady, B. (1991). A comparison of central nervous system effects of caffeine and theophylline in elderly subjects. *British Journal of Clinical Pharmacology, 32*, 341–345.

Zwyghuizen-Doorenbos, A., Roehrs, T. A., Lipschutz, L., Timms, V., & Roth, T. (1990). Effects of caffeine on alertness. *Psychopharmacology, 100*, 36–39.