

# Effects of a New Slow Release Formulation of Caffeine on EEG, Psychomotor and Cognitive Functions in Sleep-Deprived Subjects

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Caffeine is a widely-consumed psychoactive substance whose stimulant effects on mood, attention and performance are largely recognised. The central nervous system pharmacodynamic profile of a single oral dose of a new slow release (SR) caffeine formulation (600 mg) was assessed in a randomised, double-blind, crossover, placebo-controlled study. Twelve young, healthy, male, sleep-deprived (for 36 h) subjects were studied using EEG and various measures of psychomotor and cognitive functions, including critical flicker fusion (CFF), choice reaction task (CRT), tracking, continuous performance task (CPT), Stroop test, body sway and subjective evaluation (Stanford Sleepiness Scale). Caffeine significantly ( $p < 0.05$ ) antagonised the detrimental effects of sleep-deprivation on EEG (i.e. produced a significant decrease in delta and theta relative power and a significant increase in alpha and beta (12–40 Hz) relative power) and psychomotor performance (significant increase in speed of reaction on the CRT and Stroop tests, significant decrease in body sway, significant increase in accuracy of the CPT and significant reduction in subjective sedation) compared to placebo. The effect peaked 4 h after dosing and was maintained until the end of sleep deprivation (i.e. 24 h after dosing). In conclusion, the present results demonstrate that a single dose of caffeine SR possesses alerting effects which are able to reverse the deleterious effect of 36 h sleep deprivation for at least 24 h. Copyright © 2000 John Wiley & Sons, Ltd.

KEY WORDS — sleep deprivation; caffeine; humans; EEG; performance tasks

## INTRODUCTION

Caffeine is widely consumed in beverages to obtain mild central nervous system (CNS) stimulant effects. The typical caffeine content of beverages is 85–115 mg per cup of brewed coffee (175 ml), 60–65 mg per cup of instant coffee and 40–50 mg per cup of tea (Barone and Robert, 1984). It is the most widely used psychoactive drug today and is a significant component of many soft drinks and

medication (Barone and Roberts, 1996). It has been estimated that about 80 per cent of adults in the USA are regular caffeine consumers, with an average intake of approximately 200–250 mg (Barone and Roberts, 1984; Gilbert, 1984; Schreiber *et al.*, 1988).

An immediate release formulation of caffeine, as well as caffeine from beverages, has been studied using a variety of behavioural tasks for many years (for review see Weiss and Laties, 1962; Sawyer *et al.*, 1982; Dews, 1984; Lader and Bruce, 1989; Benowitz, 1990; Nehlig *et al.*, 1992; Koelega, 1993; Battig and Welzl, 1993; Sawynok, 1995). These studies showed the stimulant properties of caffeine on mood, attention and performance. Like other

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drugs of abuse, caffeine has psychoactive and reinforcing effects, its use often becomes habitual, and tolerance and discontinuation syndrome may result with repeated exposure (Griffiths and Woodson, 1988a, 1988b, 1988c; Holzman, 1990; Silverman *et al.*, 1992). Its stimulant discriminative and reinforcing effects are weak compared to amphetamines (Weiss and Laties, 1962; Dews, 1984; Koelega, 1993; Warot *et al.*, 1993) and usually its use does not become compulsive (Heischman and Henningfield, 1991, 1992).

Its effects on mood and performance are modest. Nevertheless, caffeine does have significant effects on vigilance, speed of reaction, alertness and sleep. Low and moderate doses of caffeine (20–450 mg) are usually associated with dose-dependent improvement of arousal, daytime alertness and vigilance in both sleep-deprived and fully rested individuals (Lumley *et al.*, 1987; Zwyghuizen-Doorenbos *et al.*, 1990; Walsh *et al.*, 1990; Frewer and Lader, 1991; Jarvis, 1993; Koelega, 1993; Kaplan *et al.*, 1997) and in some aspects of psychomotor performance and cognitive functions, such as reaction time, sustained attention and information processing (Clubley *et al.*, 1979; Bruce *et al.*, 1986; Liebermann *et al.*, 1987a, 1987b; Zwyghuizen-Doorenbos *et al.*, 1990; Koelega, 1993; Kaplan *et al.*, 1997), and predominantly positive subjective effects on mood characterized by increased well-being, energy and concentration (Clubley *et al.*, 1979; Liebermann *et al.*, 1987a, 1987b; Griffiths and Woodson, 1988a, 1988b, 1988c; Griffiths *et al.*, 1989, 1990; Stern *et al.*, 1989; Warot *et al.*, 1993; Kaplan *et al.*, 1997). These beneficial effects were particularly evidenced when testing occurred under conditions of caffeine deprivation or total abstinence in regular users (Griffiths *et al.*, 1989; Stern *et al.*, 1989). The acute administration of these doses increases alertness, stimulates attention and restores performance degraded by factors such as fatigue and boredom (Weiss and Laties, 1962; Lorist *et al.*, 1994) or experimental conditions used to amplify these effects such as partial or total sleep deprivation (Rosenthal *et al.*, 1991; Penetar *et al.*, 1993; Lorist *et al.*, 1994). In contrast, higher single doses are associated with more aversive effects, such as an increase in negative mood and dysphoric reactions, characterised by increases in anxiety, nervousness and tenseness. This was shown by Loke *et al.* (1985) following doses of approximately 420 mg, Chait and Griffiths (1983) after 800 mg, Roache and Griffiths (1987) after 600 mg and Kaplan (1997) after 500 mg. Tolerance to these effects may develop

over a few days after multiple doses (Griffiths and Woodson, 1988a,b,c; Zwyghuizen-Doorenbos *et al.*, 1990; Sawynok, 1995) but are incomplete (Jarvis, 1993).

Caffeine and its methylxanthine metabolites mediate their effect by binding to adenosine A1 and A2 receptors and antagonizing the effects of endogenous adenosine with the following potency profile: theophylline > caffeine > theobromine (Daly, 1982). Caffeine's inhibition constant ( $K_i$ ) values are 44 and 40  $\mu\text{mol/l}$  for A1 and A2 receptors, respectively (Daly, 1993). These concentrations correspond to the plasma concentrations encountered following consumption of normal amounts of caffeine (Sawynok, 1995). The behavioural stimulant potencies of methylxanthine correlate with their affinity for adenosine receptors (Snyder *et al.*, 1981). In vivo, caffeine treatment stimulates behavioural activity as it occupies the adenosine A1 subtype receptor (Kaplan *et al.*, 1992).

The study objective was to determine the CNS profile of a new slow release (SR) caffeine formulation on EEG and psychomotor and cognitive functions in sleep-deprived, normal subjects. A single dose safety study had shown that the maximal tolerated dose of this new formulation was 1800 mg (Gandon *et al.*, 1996). This formulation shows a delayed  $T_{\text{max}}$  (3–6 h, mean value 4 h), a lowered plasma peak concentration ( $C_{\text{max}}$ ), and a longer elimination half-life (5–8 h).

Sleep deprivation was used as a model to sensitise caffeine effects. The most notable effects of sleep deprivation are increased sleepiness and reduced alertness. Other alterations induced by sleep deprivation have been reported in mood, motivation and cognitive abilities. Sleep loss is known to diminish flexibility and preservation, to reduce motivation, to deteriorate the capacity for sustained and selective attention due to the lowering of the arousal level and to accelerate the deterioration of performance such as prolongation of reaction time and increase in errors of vigilance or choice reaction tasks over time on task (Kjellberg, 1977a, 1977b; Mikulincer *et al.*, 1989; Newhouse *et al.*, 1989; Bensimon *et al.*, 1991; Kolowsky and Babkoff, 1992; Batejat and Lagarde, 1992; Gorissen *et al.*, 1997). However, short and long term memory are not disrupted (Gorissen *et al.*, 1997). Total sleep deprivation is negatively correlated to performance and has already been successfully used as a model to assess the effects of caffeine and other stimulant drugs such as modafinil, an  $\alpha_1$  adrenergic psychostimulant (Bensimon *et al.*, 1991; Lagarde *et al.*, 1995).

## METHODS

### *Subject*

Twelve healthy young male subjects between 19 and 27 years of age (mean SD =  $28 \pm 3$  years), who weighed between 62 and 80 kg ( $70.1 \pm 6.1$  kg) and measured between 170 and 188 cm ( $178 \pm 6$  cm) in height were enrolled in the study. Their body weight did not deviate by more than 15 per cent from the Metropolitan Life Insurance Company Table. Any medication, including drugs known to be potential hepatic enzyme inducters or inhibitors, psychotropic drugs or antihistamine drugs, was prohibited from 15 days before dosing. All volunteers were screened during the 21 days preceding drug administration. All participants were declared normal after consultation of their medical histories and the results of their physical examinations, 12-lead electrocardiogram, EEG and routine laboratory tests (complete blood count, blood chemistry, urinalysis and urine drug screen for cannabis, cocaine, amphetamines, opiates and benzodiazepines). Their usual caffeine or caffeine-containing beverage consumption was less than five cups or glasses per day and they were thus not expected to have withdrawal symptoms due to caffeine deprivation. The study protocol was approved by the Ethics Committee at the University Hospital of the city of Brest (France) and written informed consent was obtained from each subject before his inclusion in the study. All types of medication were prohibited from two weeks before the study to the end of the clinical trial.

### *Study design and medication*

This was a single-centre, randomised, double-blind crossover, placebo-controlled, single-dose study consisting of two one-day treatment periods, separated by a wash-out interval of at least seven days. Subjects were randomly assigned to receive one treatment each of placebo or caffeine slow release (SR) 600 mg (two capsules of 300 mg). The compounds were administered in the presence of the investigator between 8:00 pm and 9:00 pm and were ingested with 150 ml of tap water approximately 1 h 30 min after a standardized dinner. Caffeine SR was developed by NESTEC Ltd (Nestlé Research Center, Lausanne, Switzerland).

After a night of controlled sleep (D-1) in the Clinical Pharmacology Unit, the 36-h total sleep deprivation started (on Days 1–2). Sleep deprivation

was monitored continuously by four experimenters (one physician, one research nurse and two psychologists) who were required to ensure continuous wakefulness of the subjects. On the trial day, four subjects were studied simultaneously. Between test sessions, the subjects were kept awake by verbal or physical stimulation and were allowed passive recreational activity only (i.e. talking, watching TV, reading). They were not permitted to perform activities such as playing cards, video games, etc., which could modify their level of alertness due to motivation factors. They stayed in the same ward. They were authorised to walk, to sit, but not to lie on the beds. The time course of the evaluations during each study period is summarised in Table 1.

Subjects abstained from smoking, drinking xanthine-containing beverages (coffee, tea, cola or soft drinks) or alcohol during each treatment period and the preceding 24 h. No concomitant treatment was permitted during the study. All subjects were trained before entering the trial to familiarise them with the experimental tasks and to minimise any learning effects.

### *Pharmacodynamics assessment*

The various psychometric tests and other measures (EEG, body sway) used in this study have been proved sensitive enough to assess total sleep deprivation (Batejat and Lagarde, 1992; Van Steveninck *et al.*, 1993).

*EEG recording and signal processing* Four EEG leads (right fronto-temporal F4-T4, left fronto-temporal F3-T3, right temporo-occipital T4-O2, left temporo-occipital T3-O1 according to the international 10–20 system) were recorded for 5 min under resting conditions. All the EEG recordings were performed using subcutaneous needle electrodes in a quiet room, with dimmed lighting. The subjects lay on a bed with their eyes closed under resting conditions. These conditions enhance sensitivity for measuring pharmacodynamic parameters such as onset, duration and peak activity. The reference electrode was secured to the vertex. EEG recordings were carried out with a 32-channel Enefia-type recorder (Alvar Electronic, Montreuil, France). Spectral analysis of these EEG recordings was performed using software developed by the French Army Research Centre and the Atomic Energy Commission. The four EEG channels were acquired using an Intertechnique IN-1200 com-

Table 1. Conduct of a treatment period

D-1			Hospitalisation at Biotrial Clinical Pharmacology Unit
7:30 pm			Sleep
11 pm			
D1			
7 am			Waking (Beginning of sleep deprivation)
7:45 am			Breakfast
12:30 pm			Lunch
4–7 pm			Baseline measurements CTT, CRT, SSS, CFF, Body sway, Resting EEG, ARCI, CPT, Stroop
–			Dinner
7:30 pm			Blood sample for pharmacokinetics
8:45 pm			Drug administration
9 pm	H0		
D2			
12:00 pm (midnight)	H3		CTT, CRT
12:55 am			Blood sample for pharmacokinetics
1 am	H4		SSS, CFF, Body sway, Resting EEG
3 am	H6		ARCI, CPT
4 am	H7		Stroop
5 am	H8		CTT, CRT
6 am	H9		SSS, CFF, Body sway, Resting EEG
8 am	H11		ARCI, CPT
8:30 am	H12		Breakfast
10 am	H13		CTT, CRT
11 am	H14		SSS, CFF, Body sway, Resting EEG
12:30 pm			Lunch
1 pm	H16		ARCI, CPT
2 pm	H17		Stroop
3 pm	H18		CTT, CRT
4 pm	H19		SSS, CFF, Body sway, Resting EEG
6 pm	H21		ARCI, CPT
6:30 pm			Physical examination
<i>Subjects were then taken home by taxi</i>			

ARCI: Addiction Research Center Inventory; CFF: Critical Flicker Fusion; SSS: Stanford Sleepiness Scale; CPT: Continuous Performance Task; CTT: Tracking Task; CRT: Choice Reaction Task.

puter after analogue-to-digital conversion at the rate of 200 Hz. The program then computed statistical parameters for distribution, probability density, mean moment second order to fourth order with kurtosis coefficient for epochs of 5·12 s. Artifact rejections were initially performed on the basis of amplitude to eliminate artifacts due to eye or head movements and then on the basis of standard deviation so as to preserve signal stationarity. Artifact-free 5·12-s epochs underwent spectral analysis and Fast Fourier Transform (FFT) using the Cooley Tuckey algorithm and application of Walsh ponderation. For each epoch, total energy and delta (0–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta [(12–16 Hz), (16–20 Hz), (20–30 Hz) and (30–40 Hz)] absolute and relative power were calculated and averaged.

*Critical flicker fusion (CFF)*. This test evaluates the critical flicker fusion frequency using the method of limits. This is a means of measuring the ability to distinguish discrete sensory data and is taken as an index of cortical arousal. The subject is seated and asked to maintain foveal fixation of a light source consisting of one red electroluminescent diode located at a distance of 30 cm through a tunnel. The light source is turned on intermittently at increasing then decreasing frequencies. During the increasing frequency phase, the subject is asked to press on a key when the flickering is replaced by the perception of a continuous light signal. This indicates the fusion frequency. Then, during the decreasing frequency phase, the subject indicates the frequency at which a flickering light is again perceived, i.e., the flicker frequency. These two frequencies (mea-

sured in Hertz) are relatively stable in a given subject and reliably reflect alertness and cortical arousal. The score is the mean values (in Hertz) of three increasing and three decreasing phases from 10 to 50 Hz.

*Choice reaction time (CRT)*. Sensory-motor performance was assessed using the CRT, which measures both Motor and Recognition Reaction Time as well as Total Reaction Time. The Leeds psychomotor tester was used. Subjects were required to extinguish one of six LED lights, illuminated at random, by touching the appropriate response button. The score recorded was the mean reaction time of 50 stimuli presentations.

*Critical tracking task (CTT)*. The subject uses a joystick to move a cursor horizontally on a computer screen, and attempts to keep its position matched as closely as possible to a target moving according to a computer generated complex sine wave. Tracking accuracy, in arbitrary units, was taken as the root mean square deviation of the distance of the cursor from the target. Thus, low scores reflect high accuracy.

*Continuous performance task (CPT)*. This is a sustained attention task which lasts for 20 min. At the beginning of the task, two digits, one odd and one even, are randomly chosen. The subject is then shown 1200 digits at the rate of one per second and is requested to detect 24 targets characterised by the succession of the odd followed by the even digit. The scores are the percentage of correct detections and the mean reaction time (Rosvold *et al.*, 1956).

*Body sway*. This is an objective, sensitive, reliable and non-invasive method designed to assess the effects of sedative drugs and alcohol on body sway and vigilance (McClelland, 1989). Body sway is recorded using a force-platform. Marks corresponding to the subject's foot size are fixed to the centre of the platform so that the subject's feet can be accurately repositioned in order to obtain reliable measurements. Subjects are asked to stand erect and motionless, looking at a plumbline placed in front of them. Measurements of body sway (1 min with eyes open and 1 min with eyes closed) are recorded, as recommended by the International Society of Posturography (Kapteyn *et al.*, 1983). The length and area of the postural oscillations are then calculated.

*Stroop test*. The Stroop test deals with focused attention and assesses the integrative power of cognitive mechanisms in reaching decisions based upon information from two different modalities (lexical and perceptual). First, the subjects were asked to name a colour, second, to read the name of a colour, and third, to name the printed colour of a word denoting a different colour (colour-word interference) under two conditions (simple and dual interference conditions). Subjects were instructed to perform the task as quickly and as accurately as possible. The task is believed to measure the degree to which an individual is able to successfully suppress the conflict between the two types of responses (Stroop, 1935). This test takes approximately 15 min. The main criteria were the mean reaction time and the accuracy (number of correct answers) in interference conditions for colour-word correct answers. The secondary criteria were the reaction times under colour-naming and colour-reading conditions.

*Stanford sleepiness scale (SSS)*. This is a seven-point self-rating scale of sleepiness where the investigator evaluates the most appropriate response (Hoddes *et al.*, 1973).

#### *Safety assessments*

The safety assessments were based on study event reports and the results of routine physical examinations, vital signs (blood pressure and heart rate), 12-lead ECGs and routine laboratory tests.

#### *Pharmacokinetics*

Blood samples were collected before dosing and 4 h after dosing on day 1. Caffeine and its metabolites were assayed using HPLC with liquid-solid extraction and a UV detection at 272 nm with a LOQ of 0.03 g/ml.

#### STATISTICAL ANALYSIS

Statistical analysis software SAS 6.12 release (SAS Institute Inc., Cary, NC) was used. The level was fixed at 0.05. All test hypotheses were two-tailed. The homogeneity of the baseline values was evaluated using a three-way analysis of variance (ANOVA) which tested for subject, period and treatment. Four-factor ANOVA were then performed testing for subject, period, treatment, time and time × treatment interaction on raw data or

Table 2. Summary of significant EEG changes recorded eyes closed under resting conditions after single dose of caffeine SR (600 mg) in 12 sleep-deprived young subjects

Parameter	EEG lead	Caffeine vs placebo
Total power	F4-T4, F3-T3, T4-02, T3-01	NS
Delta absolute power	F4-T4, F4-02, T3-T3, T3-01	NS
Delta relative power	F4-T4, T4-02, T3-01 F3-T3	↓(4–19 h) NS
Theta absolute power	F4-T4, T4-02, F3-T3, T3-01	NS
Theta relative power	F4-T4, T4-02, F3-T3, T3-01	↓(4–19 h)
Alpha absolute power	F4-T4, T4-02, F3-T3, T3-01	NS
Alpha relative power	F4-T4, T4-02, F3-T3, T3-01	↑(14 h)
Beta (12–16 Hz) absolute power	F4-T4, T4-02, F3-T3, T3-01	↑(4–19 h)
Beta (12–16 Hz) relative power	F4-T4, T4-02, F3-T3, T3-01	↑(4–19 h)
Beta (16–20 Hz) absolute power	F4-T4, T4-02, F3-T3, T3-01	NS
Beta (16–20 Hz) relative power	F4-T4, F3-T3 T4-02, T3-01	↑(4 h) ↑(4–19 h)
Beta (20–30 Hz) absolute power	F3-T4, T4-02, T3-01, T3-01, F3-T3	NS
Beta (20–30 Hz) relative power	F4-T4, F3-T3 T4-02 T3-01	↑(4 h) ↑(4–19 h) ↑(4–19 h)
Beta (30–40 Hz) absolute power	F4-T4, F3-T3, T3-01 T4-02	NS ↑(4 h)
Beta (30–40 Hz) relative power	F4-T4, T4-02, F3-T3, T3-01	↑(4 h)
Beta (12–40 Hz) absolute power	F4-T4, T4-02, T3-01, F3-T3	NS
Beta (12–40 Hz) relative power	F4-T4, T4-02, T3-01, F3-T3	↑(4 h)

changes from baseline when appropriate. Pairwise comparisons were done using the LSmeans method.

## RESULTS

### EEG

The summarised results of the statistical analysis are given in Table 2 and the results of delta (0–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–40 Hz) in T4-02 lead and beta (20–30 Hz) in T3-01 are given in Figures 1 and 2. There were no significant differences on baseline EEG measurements before sleep deprivation between caffeine and placebo on any EEG parameter, whatever the EEG lead. A single dose of caffeine SR 600 mg did not significantly change the total power. It produced a significant decrease in absolute delta power and in relative delta and theta power (Table 2). It also produced a significant increase in alpha relative power (T3-01, H14 only) and in beta (12–40 Hz) absolute and relative power. A trend ( $0.1 < p < 0.05$ ) to a decrease was also observed in absolute theta power (H4, H9) and a trend to an increase in absolute and relative beta power in the leads where

they were not statistically significant. The effects of caffeine were more pronounced on beta waves and thus peaked 4 h after dosing with an increase of between 100 and 200 per cent. These effects persisted up to the end of sleep deprivation (i.e. 19 h after dosing) (Figures 1 and 2). Thus, a significant improvement or trend to an improvement in alertness, as demonstrated by the increase in absolute and relative beta (12–40 Hz) power, occurred after caffeine.

### Psychomotor performance and cognitive functions

The summarised results of the statistical analysis are given in Table 3. There were no significant differences between the treatment groups on the baseline measurement done before dosing. A single dose of caffeine SR 600 mg produced significant changes in several tests compared to placebo: a significant decrease in reaction times (total and recognition choice reaction time without modifying motor time, Stroop reaction time in a non-conflictual situation), a significant increase in CPT corrects answers and a significant decrease in body sway area eyes open compared to placebo (Figure

3). In addition, no statistically significant changes were observed in the other performance tasks: increase in CFF, decrease in tracking distance, decrease in CPT average reaction time and decrease in the other body sway parameters (Figure 3). However, all these changes demonstrated a tendency towards an improvement in performance. These significant changes occurred and lasted throughout

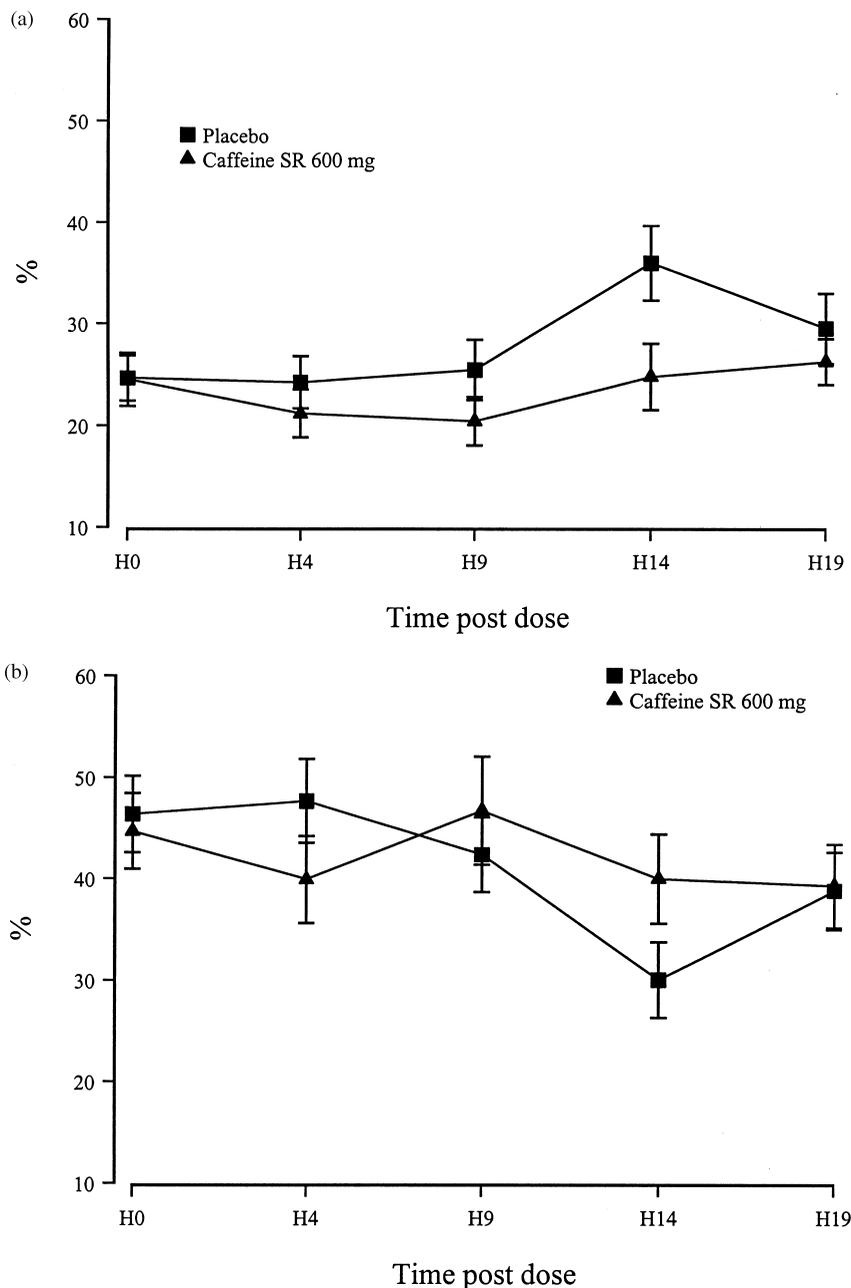


Figure 1. Delta (0–4 Hz) (a), alpha (8–12 Hz) (b), and beta (12–40 Hz) (c), relative energy recorded eyes closed under resting conditions in the T4–02 lead in 12 healthy sleep-deprived male subjects after a single oral dose of caffeine slow release (600 mg) or placebo. Results are expressed as mean  $\pm$  sem

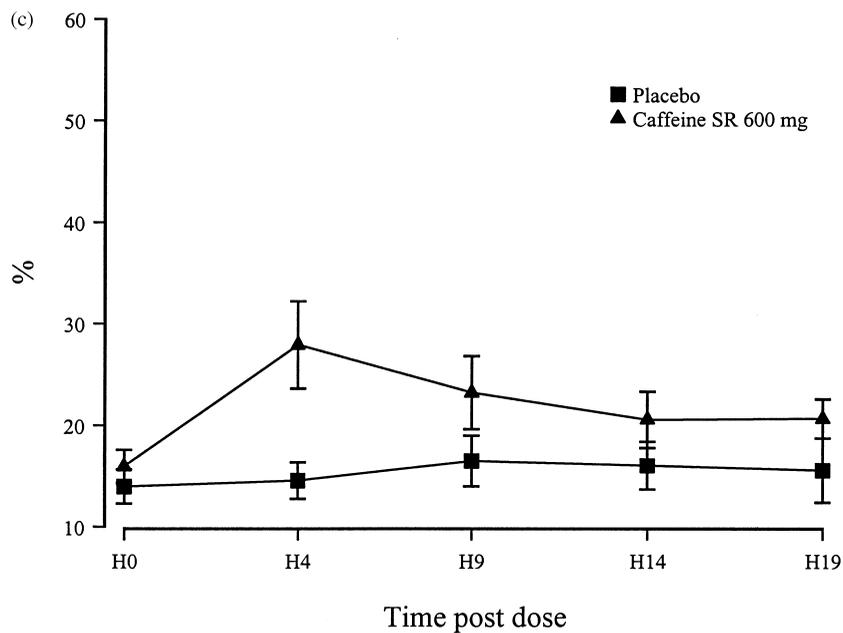


Figure 1. Continued

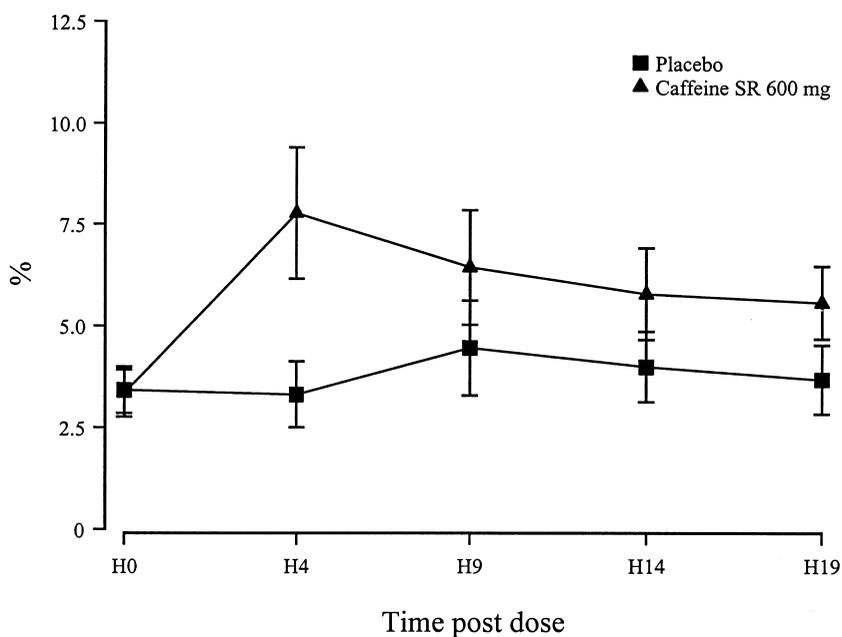


Figure 2. Beta (20–30 Hz) EEG relative energy recorded eyes closed under resting conditions in the T3–01 lead in 12 healthy sleep-deprived male subjects after a single oral dose of caffeine slow release (600 mg) or placebo. Results are expressed as mean  $\pm$  sem

Table 3. Summary of significant changes in performance and cognitive functions in 12 sleep-deprived subjects after a single dose of caffeine slow release (600 mg). Time of significant change is given in parentheses

Parameter	Caffeine vs placebo	
CFF	NS	
CRT	Total RT	↓(3–18 h)
	Recognition RT	↓(3–18 h)
	Motor RT	NS
Tracking	NS	
CPT	Accuracy	↑(6–21 h)
	RT	NS
Stroop RT	Interference	NS
	Naming	↓(7 h)
	Reading	↓(7 h)
Body sway	Area eyes open	↓(4–19 h)
	Area eyes closed	NS
	Length eyes open	NS
	Length eyes closed	NS
SSS	Sedation score	↓(4–19 h)

NS = not significant; ↑ = significant increase; ↓ = significant decrease. SSS: Stanford Sleepiness Scale; CFF: Critical Flicker Fusion; CRT: Choice Reaction Task; CPT: Continuous Performance Task; RT: Reaction Time.

the duration of sleep deprivation (from 3 to 21 h after dosing).

#### Subjective evaluation

There were no significant changes on subjective evaluation between the two treatment groups on the baseline measurement done before dosing. A single dose of caffeine SR 600 mg produced a significant reduction of the sleepiness score (Table 3, Figure 4). All subjects also felt less tired throughout the sleep deprivation period (from 4 to 21 h after dosing).

#### Safety

No serious adverse events were reported and no drop-outs for safety reasons occurred during the study. The clinical safety was satisfactory. Five emergent adverse events were reported in four subjects: two after placebo (two headaches in two subjects), and three after caffeine (one episode of

anxiety in one subject and one episode of trembling and diarrhea in another). All the subjects recovered spontaneously within 8 h. No clinically relevant changes occurred in routine laboratory tests.

#### Pharmacokinetics

The mean ( $\pm$ sem) plasma concentrations of caffeine and its metabolites obtained before dosing were similar for both treatment groups. Mean values were below 0.1  $\mu$ g/ml for caffeine, paraxanthine and theophylline and should thus be considered as negligible. Mean values of theobromine were approximately 1  $\mu$ g/ml. These are the values obtained after one day of caffeine withdrawal, because theobromine's terminal half-life is longer than that of caffeine and its other metabolites. These concentrations were very low after dosing with placebo. Four hours after caffeine SR intake, the mean  $\pm$ sem plasma concentrations were 5.48  $\pm$  0.62  $\mu$ g/ml for caffeine, 1.06  $\pm$  0.06  $\mu$ g/ml for theobromine, 0.13  $\pm$  0.01  $\mu$ g/ml for theophylline and 1.18  $\pm$  0.11  $\mu$ g/ml for paraxanthine (Table 4).

#### DISCUSSION

Caffeine SR produced a significant improvement in several EEG parameters and objective tests of performance. Caffeine significantly reduced relative slow EEG waves and significantly increased the absolute and relative EEG beta energies recorded

Table 4. Plasma concentrations of caffeine and its metabolites

	Caffeine 600 mg		Placebo	
	H0	H4	H0	H4
Caffeine ( $\mu$ g/ml)				
Mean	0.052	5.483	0.037	0.028
SD	0.081	2.149	0.041	0.046
Paraxanthine ( $\mu$ g/ml)				
Mean	0.044	1.184	0.026	0.016
SD	0.097	0.392	0.071	0.046
Theobromine ( $\mu$ g/ml)				
Mean	1.193	1.059	1.212	0.911
SD	0.351	0.221	0.606	0.482
Theophylline ( $\mu$ g/ml)				
Mean	0.030	0.125	0.028	0.021
SD	0.038	0.037	0.032	0.025

under resting conditions, especially in the 12–16 Hz and 20–30 Hz ranges. This effect occurred throughout the brain areas, peaked 4 h after dosing for the beta waves and lasted throughout the sleep deprivation period, i.e. more than 19 h after dosing.

Thus, a single dose of caffeine SR 600 mg was able to counteract the sedative EEG effects produced by sleep deprivation (increase in slow waves and decrease in fast beta waves of EEG recorded under resting conditions). In addition, caffeine SR also

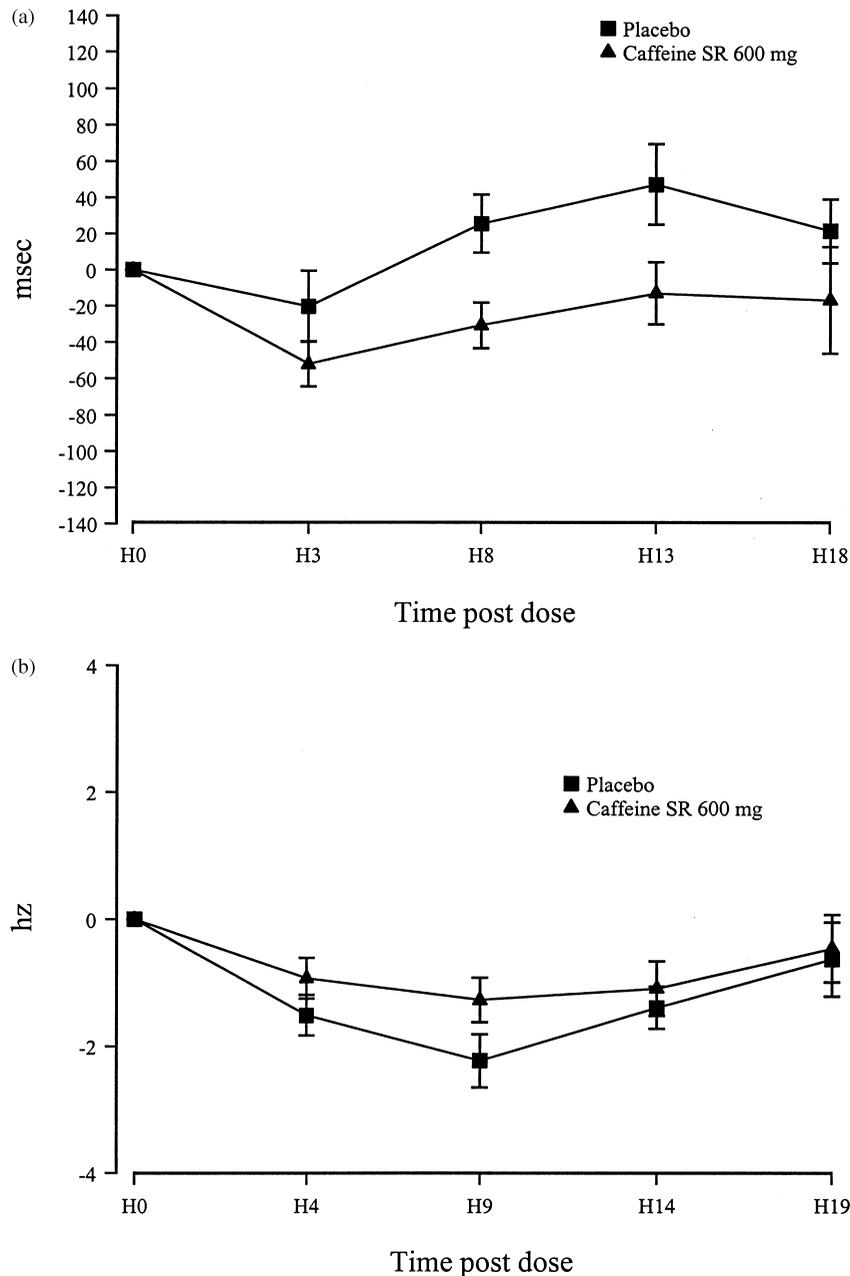


Figure 3. Effects of a single oral dose of caffeine slow release (600 mg) or placebo on choice reaction time (CRT) (a), CFF (b), tracking (c) and body sway area eyes open (d), in 12 young sleep-deprived normal subjects. Results are expressed as mean  $\pm$  sem

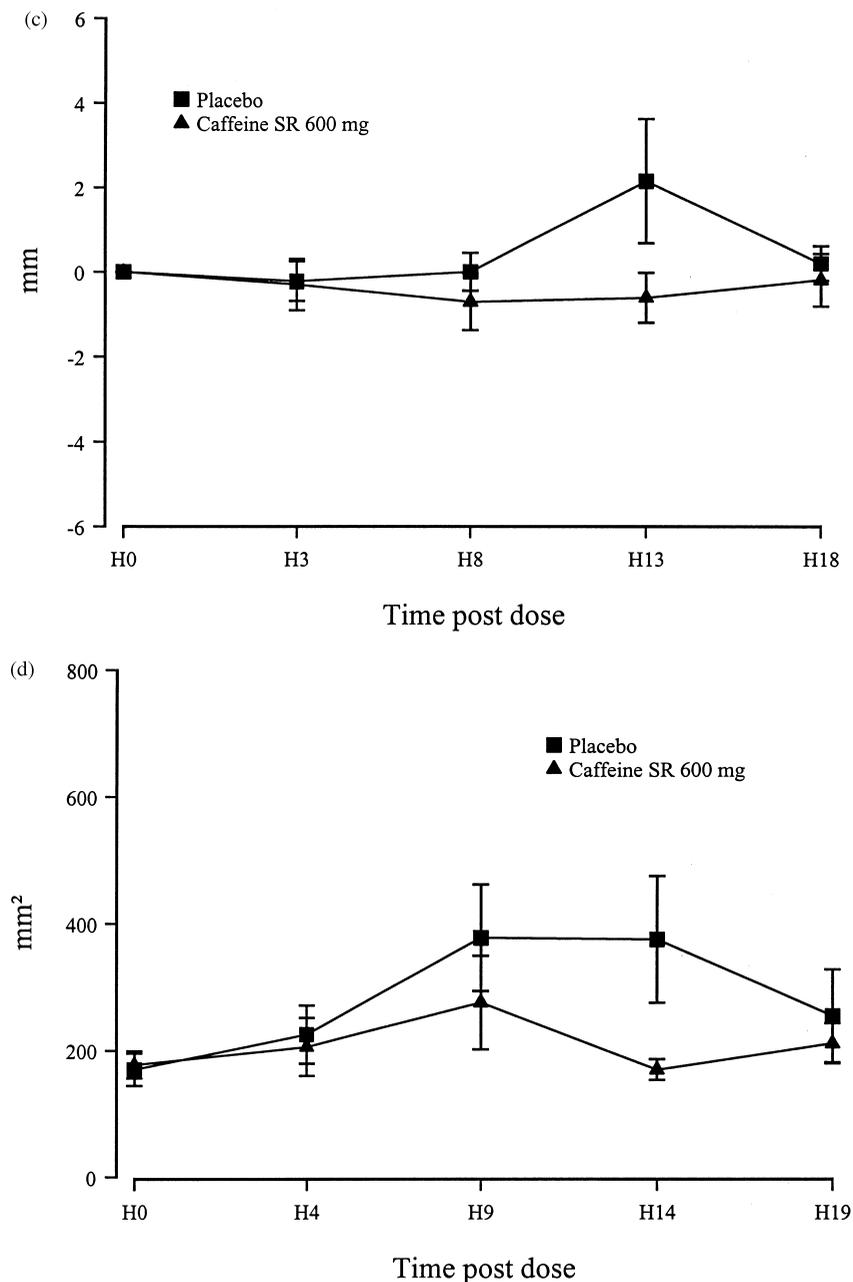


Figure 3. Continued

improved psychomotor and cognitive performance: it reduced significantly reaction times (total and recognition reaction time of the choice reaction time, Stroop reaction time), body sway area (eyes open) and accuracy (per cent of correct responses of the CPT). All the other parameters changed, even

if not significantly, in the same way, suggesting improvement: increase in CFF, decrease in tracking, decrease in CPT reaction time, and decrease in the other body sway parameters. Finally, subjects also felt less tired after caffeine on subjective evaluation (SSS score). These effects, as well as the EEG

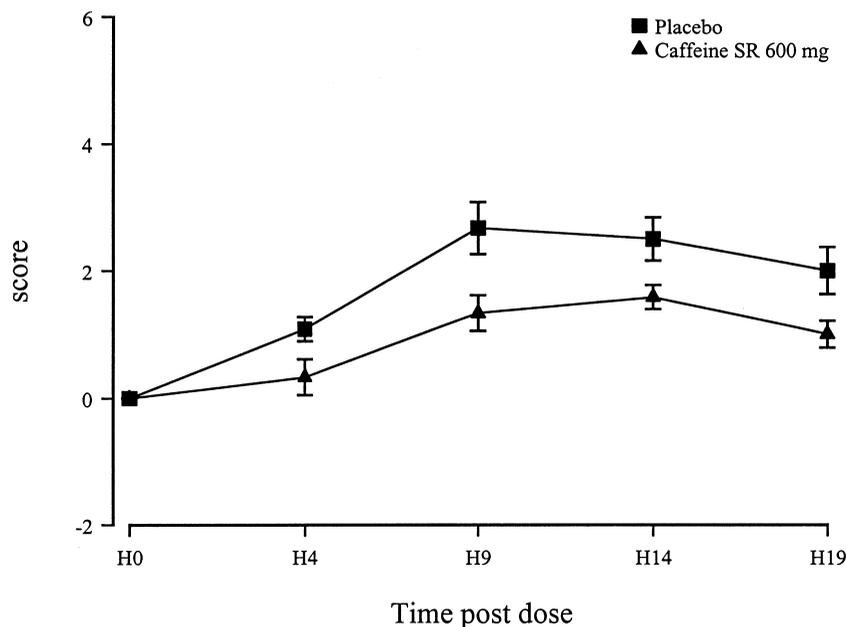


Figure 4. Effects of a single oral dose of caffeine slow release (600 mg) or placebo on the Stanford Sleepiness Scale in 12 young sleep-deprived normal subjects. A high score means more sedated. Results are expressed as mean  $\pm$  sem

effects, lasted until the end of sleep deprivation (for the 21 h duration of the assessment period after dosing). A previous study has already shown that a single dose of 600 mg slow release formulation of caffeine was able to increase subjective alertness and sleep onset latency the night after a morning dose in 120 healthy subjects (Sicard *et al.*, 1996). In addition, another study showed that a single dose of 300 and 600 mg of slow release caffeine was able to counteract the detrimental effects on performance of a 30 h sleep deprivation in 24 male and female volunteers (Lagarde *et al.*, 1996).

Finally, in another study, such a formulation at a dosage regimen of 300 mg twice daily was also shown to significantly antagonize the performance decrement in attention and cognitive performance of various tasks (cancellation task, tracking, choice reaction time etc. produced by a 64 h sleep deprivation in 16 healthy subjects. Recovery performances were not impaired (Doireau *et al.*, 1997).

The effects of caffeine on performance, attention and mood have been extensively studied in healthy well-rested volunteers. Depending on the dose level administered, a single dose of caffeine may produce either improvements or no change in certain types of behavioural tasks or in contrast more negative effects, especially on subjective scales or ques-

tionnaires in healthy volunteers. Low to intermediate doses (generally  $< 450$  mg) have been shown to significantly shorten reaction time (Clubley *et al.*, 1979; Lieberman *et al.*, 1987, 1987b; Koelega, 1993; Kaplan *et al.*, 1997), increase tapping rate (Clubley *et al.*, 1979; Kaplan *et al.*, 1997) and processing rate in DSST or Stroop or rapid visual information processing tasks (File *et al.*, 1982; Fewer and Lader, 1991; Hasenfratz and Bättig, 1992, 1994; Kaplan *et al.*, 1997) and improve vigilance on sustained attention tasks (Clubley *et al.*, 1979; Lieberman *et al.*, 1987a,b; Zwyghuisen-Doorenbos *et al.*, 1990; Frewer and Lader, 1991; Koelega, 1993). These dose levels also have positive stimulant and euphoric effects on mood and subjective evaluation, characterised by significant increases in arousal, alertness, concentration, wakefulness, energy, vigour, sense of well-being and pleasantness (Clubley *et al.*, 1979; Lieberman *et al.*, 1987a, 1987b; Stern *et al.*, 1989; Griffiths *et al.*, 1988a, 1988b, 1988c, 1989, 1990; Warot *et al.*, 1993; Hasenfratz and Bättig, 1994; Kaplan *et al.*, 1997). In contrast, higher dose levels (500 mg or more) produced some disruption in psychomotor performance as well as rather unpleasant and aversive subjective effects, including anxiety, excitement, tension, nervousness, irritability and adverse

somatic effects, such as restlessness, agitation, chills, trembling and nausea (Chait and Griffiths, 1983; Roach and Griffiths, 1987; Uhde *et al.*, 1984; Loke *et al.*, 1985; Loke, 1988; Kaplan *et al.*, 1997). High doses of caffeine (10 mg/kg) have also been shown to provoke aversive anxiogenic effects in normal subjects (Charney *et al.*, 1984; Uhde *et al.*, 1984; Mattila *et al.*, 1988; Brockwell *et al.*, 1991; Chait, 1992; Hasenfratz and Bättig, 1994) and induce even greater effects in patients with panic disorders or generalised anxiety disorders (Charney *et al.*, 1985; Bruce *et al.*, 1992).

Apart from the dose level used, some methodological issues may explain possible discrepancies between the results of studies exploring effects of single dose of caffeine in healthy young subjects on performance and showing either beneficial effects or non significant changes. Firstly, not all subjects are sensitive to the stimulant effects of caffeine. Lorist *et al.* (1994) indicated that six out of 30 subjects did not show arousing effects of caffeine. Secondly, psychomotor performance tasks are dependent upon motivation of the subject and the effect of a drug on performance could be masked by the stimulating nature of the assessment measure. Practise and learning effects must be controlled by familiarisation and training to the task prior to entry in the study. Tests of short duration are also less sensitive and effects of drugs are usually most reliably detected using a sustained task. As the task progresses, performance falls off due to boredom and fatigue and thus can be counteracted by caffeine (Weiss and Laties, 1962). Use of electrophysiological measures also improves the detection of mild effects, as these measures do not need voluntary participation of the subject and are not sensitive to motivation and training. Finally, young healthy subjects under normal conditions are already at a high level of performance and are working fairly close to their optimum performance (ceiling effect). It is thus easier to demonstrate a sedative and impairing effect than an improvement in performance.

Electrophysiological studies (EEG, multiple sleep, latency tests, event-related potentials) are useful and very sensitive to demonstrate psychostimulant effects. In man, psychostimulant agents generally increase fast beta relative power and decrease slow delta and theta relative power on EEG recorded under resting conditions. This was clearly demonstrated for amphetamines (Herrmann, 1982; Saletu, 1987; Patat *et al.*, 1996). The alerting and arousing effects of caffeine cause a shift

in EEG power towards faster components of low amplitude, characterised either by an increase in relative power spectral densities in the beta range or a shift of the dominant frequencies of the alpha and beta to higher frequencies accompanied or not by a decrease in delta, theta and alpha waves or amplitudes (Goldstein *et al.*, 1963; Bruce *et al.*, 1986; Saletu *et al.*, 1987; Etevenon *et al.*, 1986, 1989; Benowitz, 1990; Dimpfel *et al.*, 1993; Hasenfratz and Bättig, 1992, 1994; Lorist *et al.*, 1994; Smulders *et al.*, 1997). In order to better understand possible conflicting effects observed on EEG after administration of caffeine, caution must be taken in the interpretation of the data due to methodological issues. The recording conditions (either eyes closed under resting conditions or eyes closed during a vigilance task and even eyes open during a task), the electrode location and the use of monopolar or bipolar recordings (i.e. the area of the brain recorded), the expression of the results (absolute or relative power spectral densities) etc. may influence the nature of the results. Alpha activity is mainly localized on the parieto-occipital posterior part of the brain and is recorded under resting conditions eyes closed. It is a relaxed awake state which disappears when the eyes are open or when subjects concentrate on a task. In contrast, beta activity predominates over central and frontal areas on the anterior part of the brain and is more frequent with eyes open. It corresponds to alertness and concentration on a task and is thus often associated with low amplitude theta waves when recorded eyes open. Theta activity often occurs on the central and temporal areas and when recorded eyes closed under resting conditions may be linked to sleepiness. Finally, delta waves may occur on all regions and, when they predominate, correspond to sleep. Caffeine thus mainly produced a significant increase in beta (20–30 Hz) relative power, sometimes accompanied by a decrease in slow delta and theta relative powers when recorded eyes closed under resting conditions. Alpha relative power may either increase or remain unchanged. In contrast, recording during a mental or performance task (reaction time), either eyes closed or eyes open, may produce a decrease in total power as well as a decrease in some absolute energy bands, including theta, alpha and beta (Bruce *et al.*, 1986; Dimpfel *et al.*, 1993; Kaplan *et al.*, 1997). The paradoxical increase in delta absolute power observed after a single dose of caffeine by Clubley *et al.* (1979) may be explained by the small amount of caffeine (100 mg) administered, the EEG area recorded (Fz–Pz)

and the delay of EEG recording under resting condition (3 h after the intake of an immediate release caffeine formulation). Bartel *et al.* (1991) demonstrated that a single dose of 400 mg theophylline significantly reduced EEG spectral amplitude for theta, alpha and beta (13–31 Hz) bands as well as total power recorded in Oz–Cz derivation with the subjects eyes closed, compared to placebo. Analysis of the relative power values extrapolated from this paper indicates that, in contrast to absolute power, relative theta power is lower and relative beta (13–31 Hz) power is higher after theophylline than after placebo. Tolerance to these EEG effects developed over 4 weeks of treatment. Dimpfel *et al.* (1993) recorded EEG eyes open under relaxed rest and after a cognitive load condition while the subjects performed a concentration task using mapping techniques. Power spectral density was calculated for each electrode and analysis was performed using absolute power in comparison to baseline (and not to placebo) in both conditions. The course of EEG changes during the demanding situation mainly shows an increase in all frequency ranges in the occipital region and an increase in theta and beta (19–35 Hz) power in frontal areas. In addition, theta waves also increased to a lesser extent in the parietal and central areas and alpha power decreased in the frontal areas in contrast to the occipital region. This corresponds with knowledge of cortical activity under cognitive load (Rapaport-Sabag *et al.*, 1986). Administration of caffeine 200–400 mg in the relaxed state induced a decrease in absolute power in all frequency ranges of the EEG. This decrease predominates in the alpha and theta ranges in nearly all the electrodes and extended to the delta and beta waves in only a few electrodes. The effect on delta power was more pronounced with the 400 mg dose level. These findings are similar to those described by Saletu *et al.* (1987) and Benowitz (1990). The caffeine-dependent decrease in theta power and the decrease in delta power seen under relaxation conditions after 400 mg were not observed during the concentration performance test in the presence of caffeine. The power increase during the cognitive load was significantly smaller for the alpha range, but greater in the theta as well as beta (19–35 Hz) ranges (Dimpfel *et al.*, 1993). All these results show that caution is needed in the interpretation of EEG data from different assessment and data processing methods as well as different techniques of statistical analysis.

It is possible to decrease the level of performance

of the subjects either by studying fatigued or sleep deprived subjects. Sleep deprivation is negatively correlated to performance. The highest correlations have been shown with longer duration of total sleep deprivation (three nights), with speed rather than accuracy measures of performance and with work-paced rather than self-paced tasks (Kjellberg *et al.*, 1977a, 1977b; Koslowsky and Babkoff, 1992; Milkulincer *et al.*, 1989; Newhouse *et al.*, 1989; Batejat and Lagarde, 1992; Gorissen *et al.*, 1997). On the one hand, stimulation from the task seems to be a potent motivator and may counteract the effects of total sleep deprivation. On the other hand, prolonged monotonous and/or continuous tasks (such as auditory vigilance or continuous performance task, or highly demanding cognitive tasks) are sensitive to even one night of total sleep deprivation (Glenville *et al.*, 1978; Horne and Pettitt, 1985; Wimmer *et al.*, 1992). Neurophysiological measurements, such as quantitative EEG or body sway, which are not influenced by training or motivation, are also highly sensitive to total sleep deprivation. The main deprivation effects on all vigilance parameters occurred mainly at night rather than during the day. Circadian rise in performance during the day may counteract the fall due to total sleep deprivation, with both effects being additive at night (Batejat and Lagarde, 1992; Marks and Folkhard, 1984). The return to normal values occurred rapidly, usually after an 8-h recovery of sleep. Total sleep deprivation was used in this study as a model to assess the alerting effects of caffeine SR. Indeed, larger improvements have already been demonstrated after caffeine on various performance tasks, including choice-reaction task, sustained attention task, on MSLT, on EEG and on event-related potentials after fatigue or partial or total sleep deprivation than in well-rested subjects (Weiss and Laties, 1962; Rosenthal *et al.*, 1991; Lorist *et al.*, 1994; Penetar *et al.*, 1993).

Another way to produce an artificial decrement in performance in healthy young volunteers is to administer sedative drugs such as benzodiazepines. Caffeine was shown to counteract the effects of benzodiazepine on mood, attention and sensorimotor coordination. Caffeine 75–250 mg reversed the effects of lorazepam 2.5 mg on DSST, symbol copying and subjective relaxation and calm measured by visual analogue scales, but not its effects on a cancellation task or a verbal learning memory task (File *et al.*, 1982). Caffeine 200–500 mg was also shown to antagonise the deleterious effects of diazepam 10–20 mg on DSST, muscle relaxation

measured by Maddox wing, critical flicker fusion, as well as subjective calmness and sedation (Mattila *et al.*, 1982; Ghoneim *et al.*, 1986; Loke *et al.*, 1985; Roache and Griffiths, 1987). Finally, Johnson *et al.* (1990a, 1990b) demonstrated that caffeine 250 mg taken early in the morning is able to significantly antagonized next day hypnotic-induced drowsiness in subjects treated by flurazepam (30 mg) or triazolam (0.5 mg) and enhanced alertness in the subjects who received bed-time placebo. These effects on daytime sleepiness were evidenced on multiple sleep latency tasks as well as on subjective evaluation (Stanford Sleepiness Scale). Caffeine also reduced the performance impairment on psychomotor task (DSST, choice reaction time) produced by these hypnotics, but the improvement in performance was not statistically significant.

Finally, caffeine was shown to decrease sleepiness in increasing latencies to sleep onset and to improve daytime alertness as measured by multiple sleep latency (MSLT) tasks in both sleep-deprived and fully rested subjects (Lumley *et al.*, 1987; Zwyghuizen-Doorenbos *et al.*, 1990; Walsh *et al.*, 1990; Penetar *et al.*, 1993).

All these published data, using either electrophysiological methods (EEG, MSLT), various tests exploring attention, vigilance or psychomotor performance and information processing or subjective evaluation of sedation, clearly showed beneficial alerting properties of caffeine taken either as a beverage or as an immediate release formulation, especially in the dose range between 100 and 400 mg. The present results demonstrate that a single dose of a new slow release formulation of caffeine developed by NESTEC Ltd possesses alerting effects able to reverse the deleterious effects on EEG and various performance tasks of sleep deprivation and to maintain performance during limited (36 h) sleep deprivation. Potential use concerns the treatment of jet lag syndrome and the pharmacological management of limited sleep deprivation or extended duty. It may thus be useful in several situations where vigilance must be maintained, for instance, when driving.

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#### REFERENCES

- Barone JJ, Roberts H. 1984. Human consumption of caffeine. In *Caffeine: Perspectives from Recent Research*, Dews PB (ed.). Springer: New York; 57–73.
- Barone JJ, Roberts HR. 1996. Caffeine consumption. *Food Chem Toxicol* **34**: 119–129.
- Bartel P, Delpont R, Lotz B, Ubbink J, Becker P. 1991. Effects of single and repeated doses of theophylline on aspects of performance, electrophysiology and subjective assessments in healthy human subjects. *Psychopharmacology* **106**: 90–96.
- Batejat D, Lagarde D. 1992. Circadian rhythm and sleep deprivation: effects on psychomotor performance. *Med Sci Res* **20**: 167–168.
- Battig K, Welzl H. 1993. Psychopharmacological profile of caffeine. In *Caffeine Coffee and Health*, Garrattini S (ed.). Raven Press: New York; 213–253.
- Benowitz NL. 1990. Clinical pharmacology of caffeine. *Ann Rev Med* **41**: 227–288.
- Bensimon G, Benoit D, Lacomblez L, Weiller E, Warot D, Weil JS, Puech AJ. 1991. Antagonism by modafinil of the psychomotor and cognitive impairment induced by sleep deprivation in 12 healthy volunteers. *Eur Psychiat* **6**: 93–97.
- Brockwell NT, Eikelboom R, Beninger RJ. 1991. Caffeine-induced place and taste conditioning: production of dose-dependent preference and aversion. *Pharmacol Biochem Behav* **38**: 513–517.
- Bruce M, Scott N, Lader M, Marks V. 1986. The psychopharmacological and electrophysiological effects of single doses of caffeine in healthy human subjects. *Br J Clin Pharmacol* **22**: 81–87.
- Bruce M, Scott N, Shine P, Lader M. 1992. Anxiogenic effects of caffeine in patients with anxiety disorders. *Arch Gen Psychiat* **49**: 867–869.
- Chait LD. 1992. Factors influencing the subjective response to caffeine. *Behav Pharmacol* **3**: 219–228.
- Chait LD, Griffiths PR. 1983. Effects of caffeine on cigarette smoking and subjective response. *Clin Pharmacol Therapeut* **34**: 612–622.
- Charney DS, Galloway MP, Heninger GR. 1984. The effects of caffeine on plasma MHPG, subjective anxiety, autonomic symptoms and blood pressure in healthy humans. *Life Sci* **35**: 135–144.
- Charney DS, Heninger GR, Jatlow PI. 1985. Increased anxiogenic effects of caffeine in panic disorders. *Arch Gen Psychiat* **42**: 233–243.
- Clubley M, Bye CE, Henson TA, Peck AW, Riddington CJ. 1979. Effects of caffeine and cyclizine alone and in combination on human performance, subjective effects and EEG activity. *Br J Clin Pharmacol* **7**: 157–163.
- Daly JW. 1982. Adenosine receptors: targets for future drugs. *J Med Chem* **25**: 197–207.

- Daly JW. 1993. Mechanism of action of caffeine. In: *Caffeine, Coffee and Health*, Garattini S. (ed.). Raven Press: New York; 97–150.
- Dews PB. 1984. Behavioural effects of caffeine. In: *Caffeine*, Dews PB (ed.). Springer: New York; 86–103.
- Dimpfel W, Schober F, Spuler M. 1993. The influence of caffeine on human EEG under resting conditions and during mental loads. *Clin Invest* **71**: 197–207.
- Doireau P, Batejat D, Chauffard F, Enslin M, Tachon P, Pradella S, Lagarde D. 1997. Cognitive performance during a 64 hours sleep deprivation: interest of a slow release caffeine. NATO-RTA-AMP meeting (29 Sept–3 Oct 1997) Rotterdam.
- Etevenon P, Peron-Magnan P, Boulenger JP, Tortrat D, Guillot S, Toussaint M, Gueguen B, Deniker P, Zarifian E. 1986. EEG cartography profile of caffeine in normals. *Clin Neuropharmacol* **9**: 538–540.
- 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 cartography of caffeine effects in normals. In: *Brain imaging: applications in psychiatry*, Andreasen NC (ed.). American Psychiatric Press: Washington, DC; 171–180.
- File SE, Bond AJ, Lister RG. 1982. Interaction between effects of caffeine and lorazepam in performance tests and self-ratings. *J Clin Psychopharmacol* **2**(2): 102–106.
- Frewer LJ, Lader M. 1991. The effects of caffeine on two computerized tests of attention and vigilance. *Human Psychopharmacol* **6**: 119–128.
- Gandon JM, Le Coz F, Enslin F, Chauffard P, Tachon P, Allain H, Patat A. 1996. Determination of the maximal tolerated dose of a new acute oral caffeine formulation in healthy volunteers. *Clin Pharmacol Therapeut* **59**: 179.
- Ghoneim MM, Hinrichs HV, Chiang CK, Loke WH. 1986. Pharmacokinetic and pharmacodynamic interactions between caffeine and diazepam. *J Clin Psychopharmacol* **6**: 75–80.
- Gilbert RM. 1984. Caffeine consumption. In: *The methylxanthine beverages and foods: chemistry, composition and health effects*, Spiller GA (ed.). Liss: New York; 185–213.
- Glenville M, Broughton R, Wing AM, Wilkinson RT. 1978. Effects of sleep deprivation on short duration performance measures compared to the Wilkinson Auditory Vigilance Task. *Sleep* **11**(2): 169–176.
- Goldstein L, Muphee HB, Pfeiffer CC. 1963. Quantitative electroencephalography in man as a measure of CNS stimulation. *Ann NY Acad Sci* **107**: 1045–1056.
- Gorissen M, Tieleman M, Coenen A. 1997. Alertness and memory after sleep deprivation and diazepam intake. *J Psychopharmacol* **11**(3): 233–239.
- Griffiths RR, Woodson PP. 1988a. Caffeine physical dependence: a review of human and laboratory animal studies. *Psychopharmacol* **94**: 437–451.
- Griffiths RR, Woodson PP. 1988b. Reinforcing effects of caffeine in humans. *J Pharmacol Exp Therapeut* **246**: 21–29.
- Griffiths RR, Woodson PP. 1988c. Reinforcing properties of caffeine: studies in humans and laboratory animals. *Pharmacol Biochem Behav* **29**: 419–427.
- Griffiths RR, Bigelow GE, Liebson IA. 1989. Reinforcing effects of caffeine in coffee and capsules. *J Exp Analyt Behav* **52**: 127–140.
- Griffiths RR, Evans SM, Heishman SJ, Preston KL, Sannerud CA, Wolf B, Woodson PP. 1990. Low-dose caffeine discrimination in humans. *J Pharmacol Exp Therapeut* **252**: 970–978.
- Hasenfratz M, Bättig K. 1992. Action profiles of smoking and caffeine: Stroop effect, EEG, and peripheral physiology. *Pharmacol Biochem Behav* **42**: 155–161.
- Hasenfratz M, Bättig K. 1994. Acute dose-effect relationships of caffeine and mental performance, EEG, cardiovascular and subjective parameters. *Psychopharmacol* **114**: 281–287.
- Heischman SJ, Henningfield JE. 1991. Discriminative stimulus effects of d-amphetamine, methylphenidate, and diazepam in humans. *Psychopharmacol* **103**: 436–442.
- Heischman SJ, Henningfield JE. 1992. Stimulus functions of caffeine in humans: relation to dependence potential. *Neurosci Biobehav Rev* **16**: 273–287.
- Herrmann WM. 1982. Development and critical evaluation of an objective procedure for the electroencephalographic classification of psychotropic drugs. In *EEG in Drug Research*, Hermann W. (ed.). Gustav Fischer Verlag: Stuttgart; 249–351.
- Hoddes E, Zarcone V, Smythe H, Philips R, Dement WC. 1973. Stanford sleepiness scale. Quantification of sleepiness: a new approach. *Psychophysiol* **10**: 431–436.
- Holzman S. 1990. Caffeine as a model drug of abuse. *Trends Pharmacol Sci* **11**: 355–356.
- Horne JA, Pettitt AN. 1985. High incentive effects on vigilance performance during 72 hours of total sleep deprivation. *Acta Psychol* **58**: 123–139.
- Jarvis MJC. 1993. Does caffeine intake enhance absolute levels of cognitive performance? *Psychopharmacol* **110**: 45–52.
- Johnson LC, Spinweber CL, Gomez SA. 1990a. Benzodiazepines and caffeine: effect on daytime sleepiness, performance and mood. *Psychopharmacol* **101**: 160–167.
- Johnson LC, Spinweber CL, Gomez SA, Matteson LT. 1990b. Daytime sleepiness, performance, mood, nocturnal sleep: the effect of benzodiazepine and caffeine on their relationship. *Sleep* **13**(2): 121–135.
- Kaplan GB, Greenblatt DJ, Kent MA, Cotreau MM, Arcelin G, Shader RI. 1992. Caffeine-induced behavioural stimulation is dose-dependent and associated with A1 adenosine receptor occupancy. *Neuropsychopharmacol* **6**: 145–153.
- Kaplan GB, Greenblatt DJ, Ehrenberg BL, Goddard JE, Cotreau MM, Harmatz JS, Shader RI. 1997. Dose-

- dependent pharmacokinetic and psychomotor effects of caffeine in humans. *J Clin Pharmacol* **37**: 693–703.
- Kapteyn TS, Bles W, Nijokiktjein CJ, Kodde L, Massen CH, Mol JMF. 1983. Standardisation in platform stabilometry being part of posturography. *Agressologie* **24**: 321–326.
- Kjelberg A. 1977a. Sleep deprivation and some aspects of performance. II. Lapses and other attentional effects. *Waking and Sleeping* **1**: 145–148.
- Kjelberg A. 1977b. Sleep deprivation and some aspects of performance. III. Motivation, Comment and Conclusions. *Waking and Sleeping* **1**: 149–153.
- Koelega HS. 1993. Stimulant drugs and vigilance performance: a review. *Psychopharmacol* **111**: 1–16.
- Koslowsky M, Babkoff H. 1992. Meta-analysis of the relationship between total sleep deprivation and performance. *Chronobiol Int* **9**(2): 132–136.
- Lader MH, Bruce MS. 1989. The human psychopharmacology of the methylxanthines. In: *Human Psychopharmacology: Measures and Methods*, Hindmarch I, Stonier PD (eds). John Wiley: Chichester; 179–200.
- Lagarde D, Batejat D, VAN Beers P, Sarafian D, Pradella S. 1995. Interest of modafinil, a new psychostimulant, during a sixty-hour sleep deprivation experiment. *Fundamental Clin Pharmacol* **9**: 271–279.
- Lagarde D, Batejat D, Enslin M, Chauffard F, Tachon P. 1996. Interest of a new time release caffeine to maintain psychomotor performance. *J Sleep Res* **5**, 1: 115.
- Liebermann HR, Wurtman RJ, Emde GG, Roberts C, Coviella ILG. 1987a. The effects of low doses of caffeine on human performance and mood. *Psychopharmacol* **92**: 308–312.
- Liebermann FR, Wurtman RJ, Emde GC, Coviella ILG. 1987b. The effects of caffeine and aspirin on mood and performance. *J Clin Psychopharmacol* **7**: 315–320.
- Loke WH. 1988. Effects of caffeine on mood and memory. *Physiol Behav* **44**: 367–372.
- Loke WH, Hinrichs JV, Ghoneim MM. 1985. Caffeine and diazepam: separate and combined effects on mood, memory, and psychomotor performance. *Psychopharmacol* **87**: 344–350.
- Lorist MM, Snel J, Kok A. 1994. Influence of caffeine on information processing stages in well rested and fatigued subjects. *Psychopharmacol* **113**: 411–421.
- Lumley M, Roehrs T, Asker D, Zorick F, Roth T. 1987. Ethanol and caffeine effects on daytime sleepiness/alertness. *Sleep* **10**: 306–312.
- Marks M, Folkard S. 1984. Diurnal rhythms in cognitive performance. In: *Psychology Survey*, Vol. 5, Nicholson J, Beloff H. (eds). British Psychological Society: Leicester; 63–94.
- Mattila MJ, Palva E, Savolainen K. 1982. Caffeine antagonizes diazepam effects in man. *Med Biol* **60**: 121–123.
- Mattila M, Seppala T, Mattila MJ. 1988. Anxiogenic effect of yohimbine in healthy subjects: comparison with caffeine and antagonism by clonidine and diazepam. *Int J Clin Pharmacol* **3**: 215–229.
- McClelland GR. 1989. Body sway and the effects of psychoactive drugs—a review. *Human Psychopharmacol* **4**: 3–14.
- Mikulincer M, Babkoff H, Capsy T, Sing H. 1989. The effects of 72 hours of sleep loss on psychological variables. *Br J Psychol* **80**: 145–162.
- Nehlig A, Daval JL, Debry G. 1992. Caffeine and the central nervous system: mechanisms of action, biochemical, metabolic and psychostimulant effects. *Brain Res Rev* **17**: 139–170.
- Newhouse PA, Belenky, Thomas M, Thorne D, Sing HC, Fertig J. 1989. The effects on d-amphetamine on arousal, cognition, and mood after prolonged total sleep deprivation. *Neuropsychopharmacol* **2**: 153–164.
- Patat A, Cercle M, Trocherie S, Peytavin G, Potin C, Allain H, Gandon JM. 1996. Lack of amphetamine-like effects after administration of mefenorex in normal young subjects. *Human Psychopharmacol* **2**: 321–335.
- 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. *Psychopharmacol* **112**: 359–365.
- Rappelsberger P, Pockberger H, Petsche H. 1986. Computer aided EEG analysis—evaluation of changes during cognitive processes and topographic mapping. *EDV Med Biol* **17**: 45–53.
- Roache JD, Griffiths RR. 1987. Interactions of diazepam and caffeine: behavioural and subjective dose effects in humans. *Pharmacol Biochem Behav* **26**: 801–812.
- Rosenthal L, Roehrs T, Zwyghuizen-Doorenbos A, Plath D, Roth T. 1991. Alerting effects of caffeine after normal and restricted sleep. *Neuropsychopharmacol* **4**(2): 103–108.
- Rosvold ME, Mirsky AF, Sarason I, Bransome ER Jr, Beck LH. 1956. A continuous performance test for brain damage. *J Consult Psychol* **20**(5): 343–350.
- Saletu B. 1987. The use of pharmaco-EEG in drug profiling. In: *Human Psychopharmacology: Measures and Methods*, Hindmarch I, Stonier PD. (eds). John Wiley and Sons: Chichester; 177–200.
- Saletu B, Anderer P, Kinsberger K, Grunberger J. 1987. Topographic brain mapping of EEG in neuropsychopharmacology. Clinical applications (pharmaco EEG imaging). *Methods Findings Exp Clin Pharmacol* **9**: 385–408.
- Sawyer DA, Julia HL, Turin AC. 1982. Caffeine and human behavior: arousal, anxiety and performance effects. *J Behav Med* **5**(4): 415–439.
- Sawynok J. 1995. Pharmacological rationale for the clinical use of caffeine. *Drugs* **49**: 37–50.
- Schreiber GB, Maffeo CE, Robins M. 1988. Measurement of coffee and caffeine intake: implications for epidemiological research. *Prevent Med* **17**: 280–294.
- Sicard B, Perault MC, Enslin M, Chauffard F, Vandel B, Tachon P. 1996. The effects of 600 mg of slow release caffeine on mood and alertness. *Aviation, Space Environ Med* **67**(9): 859–862.
- Silverman K, Evans SM, Strain EC, Griffiths RR. 1992.

- Withdrawal syndrome after the double-blind cessation of caffeine consumption. *New England J Med* **327**: 1109–1114.
- Smulders FT, Kenemans JL, Jonkman LM, Kok A. 1997. The effects of sleep loss on task performance and the electroencephalogram in young and elderly subjects. *Biol Psychol* **45**: 217–239.
- Snyder SH, Katims JJ, Annau Z, Bruns RF, Daly JW. 1981. Adenosine receptors and behavioral actions of methylxanthines. *Proc Nat Acad Sci USA* **78**: 3260–3264.
- Stern KN, Chait LD, Johanson CE. 1989. Reinforcing and subjective effects of caffeine in normal human volunteers. *Psychopharmacol* **98**: 81–88.
- Stroop JR. 1935. Studies of interference in serial verbal reactions. *J Exp Psychol* **18**: 643–662.
- Uhde TW, Boulenger JP, Jimerson DC, Post RM. 1984. Caffeine: relationship to human anxiety, plasma MHPG, and cortisol. *Psychopharmacol Bull* **20**: 426–430.
- Van Steveninck AL, Van Berckel BNM, Schoemaker HC, Breimer DD, Cohen AF. 1993. Sensitivity of CNS performance tests to the effects of sleep deprivation. *Br J Clin Pharmacol* **35**(5): 551P.
- Walsh JK, Muehlbach MJ, Humm TM, Dickins QS, Sugerman JL, Schweitzer PK. 1990. Effects of caffeine on physiological sleep tendency and ability to sustain wakefulness at night. *Psychopharmacol* **101**: 271–273.
- Warot D, Corruble E, Payan C, Weil JS, Puech AJ. 1993. Subjective effects of modafinil, a new central adrenergic stimulant in healthy volunteers: a comparison with amphetamine, caffeine and placebo. *Eur Psychiat* **8**: 201–208.
- Weiss B, Laties VG. 1962. Enhancement of human performance by caffeine and the amphetamines. *Pharmacol Rev* **14**: 1–36.
- Wimmer F, Hoffmann RF, Bonato RA, Moffitt AR. 1992. The effects of sleep deprivation on divergent thinking and attention processes. *J Sleep Res* **1**: 223–230.
- Zwyghuizen-Doorenbos A, Roehrs TA, Lipschuts L, Timms V, Roth T. 1990. Effects of caffeine on alertness. *Psychopharmacol* **100**: 36–39.