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Effects of repeated doses of caffeine on mood and performance of alert and fatigued volunteers

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Abstract

Evidence for behavioural effects of caffeine is well documented in the literature. It is associated with increased subjective alertness, improved reaction time and enhanced encoding of new information. These effects are most prominent in low arousal situations. However, there is an ongoing debate as to whether such changes are in fact improvements or merely a reversal of the negative effects of a period of caffeine withdrawal (e.g. overnight abstinence). To avoid such a confound this study included multiple doses of caffeine which were administered under double-blind conditions to participants who had ingested their normal daily quota of caffeine. In the present study participants were fatigued by carrying out a prolonged testing schedule in the evening. Sixty volunteers, all regular caffeine consumers, took part in the study. They attended for three sessions on separate days. They were instructed to consume normal amounts of caffeinated beverages. Consumption was measured by a diary and saliva samples were taken and caffeine assays conducted. A baseline test session was carried out at 18.00 h and following this a double blind placebo controlled caffeine challenge (1.5 mg/kg) conducted. The test battery was repeated twice approximately 30 minutes after the caffeine challenge. Following this another drink was administered and the test battery repeated twice more. On one test session volunteers had placebo in both drinks, in another they had caffeine in both drinks and another caffeine in the first and placebo in the second. Order of conditions was balanced across subjects. The results showed that caffeine led to a more positive mood and improved performance on a number of tasks. Different effects of caffeine were seen depending on the person's level of arousal. Linear effects of caffeine dose were also observed. This is evidence against the argument that behavioural changes due to caffeine are merely the reversal of negative effects of a long period of caffeine abstinence. The findings are discussed in relation to both noradrenergic and cholinergic neurotransmitter systems.

Keywords
arousal, caffeine, psychomotor performance, mood, psychopharmacology

Introduction

It is now well established that ingestion of caffeine is associated with increases in alertness and improved sustained attention and psychomotor performance (see reviews by Lieberman, 1992; Smith, 2002, 2005). Given that alertness often increases following caffeine ingestion, it is not surprising that the effects of caffeine are most easily observed in low arousal situations (e.g., at night – Smith *et al.*, 1993; after lunch – Smith *et al.*, 1991; when the person is sleep deprived – Bonnet *et al.*, 1995; when the person has a cold – Smith, Thomas *et al.*, 1997). In addition, simulations of real-life activities such as driving have shown that caffeine may benefit the sleepy driver (Horne and Reyner, 1996) and such information has been incorporated into practical guidelines such as the United Kingdom Highway Code.

Recent research has also begun to address the nature of the mechanisms underlying the behavioural effects of caffeine. Smith *et al.* (2003) found that clonidine (a noradrenaline antagonist that mimics natural low arousal states such as sleep deprivation) increased response times in a simple reaction time (SRT) task, and that this could be reversed by caffeine administration. Clonidine also increased the number of long response times (>1500 ms) in a choice reaction time task; these long responses are an indication of momentary lapses of attention (Smith and Nutt, 1996) and were also reduced following caffeine administration. In addition, the same study also showed effects of caffeine that were independent of clonidine: caffeine improved both speed of encoding in a choice reaction time task and reduced response times in a cognitive vigilance task, regardless of whether volunteers received clonidine or placebo. These latter effects are thought to reflect increases in

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cholinergic activity; thus, it is argued, these data suggest that the effects of caffeine in non-fatigued volunteers mainly reflect changes in acetylcholine (ACh), whereas additional effects seen in fatigued volunteers relate to changes in noradrenaline (NA).

James (1994) has argued that caffeine has no beneficial effects on cognitive performance per se, but merely removes negative effects produced by a period of caffeine withdrawal (e.g. overnight abstinence). One method of addressing this issue is to examine the effects of caffeine in volunteers who have been allowed to consume caffeinated products prior to testing and have not had caffeine withdrawn for a long period. In a previous study (Christopher *et al*., 2005) we found improvements in mood (self-report alertness) and cognitive performance (speed of encoding and cognitive vigilance) following caffeine ingestion in volunteers who had not had caffeine withdrawn overnight. These effects were interpreted in terms of caffeine-induced increases in cortical ACh in volunteers who were relatively alert and non-fatigued: According to Warburton *et al.* (2001) caffeine reduces the normal fluctuations in arousal that occur in situations requiring sustained attention, and this effect may be mediated by cholinergic projections from brain stem nuclei to the cortex.

Another way to test the withdrawal hypothesis is by using multiple doses of caffeine and determining whether any effects are cumulative. Assuming that the first dose is sufficient to reverse any withdrawal effects, a subsequent dose should not produce any further improvements in task performance. Recent studies addressing this issue have produced mixed findings. Jarvis (1993) reported a trend for improved cognitive performance with increasing levels of caffeine consumption in a naturalistic survey of over 9000 volunteers. However, some more controlled studies, where multiple doses of caffeine are administered by the experimenter, have reported no effect of caffeine after the first dose, a finding which is consistent with the withdrawal hypothesis (Robelin and Rogers, 1998; Yeomans *et al.*, 2002).

One aim of the present study, therefore, was to examine the effects of consecutive doses of caffeine in volunteers who had followed their normal pattern of daily caffeine consumption. A second aim was to test volunteers over a much longer time period than in our previous study, in order to investigate further the hypothesis that specific behavioural effects of caffeine depend on the person's underlying state of arousal. Thus, we predicted that at the start of the test session (when volunteers were relatively alert) caffeine would produce the same effects as were seen in our previous study (i.e., increased alertness, faster encoding of information, improved vigilance performance), and that additional effects (faster SRT, fewer long responses) would become evident as volunteers became more fatigued because of prolonged testing and declining circadian alertness. Finally, the study examined whether linear-dose related effects of caffeine were observed as volunteers became more fatigued. Previous studies of effects of consecutive doses of caffeine have usually given the first dose in the early morning and the second dose mid-morning. Circadian alertness increases over the morning and this may have masked any alerting effects of the second dose of caffeine. This was avoided here by giving the second dose at a time when volunteers were becoming more fatigued due to prolonged testing and declining circadian alertness. In addition, the study used doses that are relevant to typical dietary intakes and gave the caffeine in beverages in which caffeine is normally present (although previous research suggests that the nature of the vehicle in which the caffeine is administered is relatively unimportant, Smith *et al*., 1999).

Method

This study was approved by the Ethics Committee of the School of Psychology, Cardiff University, and carried out with the informed consent of the volunteers.

Participants

Studies investigating the effects of caffeine in alert individuals show an effect size of 0.8 SD which translates into a minimum sample size of 24 participants per group to identify effects. In situations where levels of alertness are reduced caffeine effects are usually much larger and can be measured in much smaller samples (between 10 and 12 participants per group, e.g., Bonnet and Arand, 1994). Sixty volunteers (18 male, 42 female; mean age 21, age range 18 to 44 years; mean body weight = 66.3 kg, range = 41–107 kg)) were recruited from the student recruitment panel in the Centre for Occupational and Health Psychology at Cardiff University. All participants were full-time students and were paid £50 for taking part. Individuals were excluded from the study if they did not consume caffeine on a daily basis.

Design

Caffeine manipulations occurred within subjects using a placebo-controlled double blind procedure. Each volunteer was tested on three different days and the amount of caffeine administered during each visit varied. On completion of the study, each volunteer had received the following doses of caffeine: (a) 0 mg/kg (PP, i.e., placebo in both drinks); (b) 1.5 mg/kg (CP, i.e., caffeine in the first drink and placebo in the second); (c) 3.0 mg/kg (CC, i.e., caffeine in both drinks). Condition order was counter-balanced across participants.

Procedure

Schedule of testing

Prior to the test day, participants were familiarized with the experimental procedure and given a practice session on the tasks. At this familiarization session participants were also required to read an information sheet and sign a consent form. After practising the computerized task battery, participants were reminded of the requirements for the test day (a limit of four units of alcohol on the evening prior to testing, no alcohol consumption during the test day and no vigorous exercise on the test day).

Following familiarization, participants attended test sessions on three separate days. Each session ran from 18:00 h to approximately 22:00 h. On arriving (18:00) volunteers recorded all drinks they had consumed that day. Saliva samples were also taken and these were sent to the University of Surrey to be assayed for caffeine using an ELISA (Fickling *et al.*, 1990). The first battery of tasks (lasting approximately 30 minutes) was then completed; these provided baseline measures which were used as covariates in subsequent analyses of covariance (ANCOVA). Following the first task battery, volunteers were given a 300 ml cup of decaffeinated coffee or tea to which had been added either 1.5 mg/kg caffeine or placebo. Thirty minutes after finishing the drink, participants completed the task battery twice over (i.e., an hour of continuous testing). Saliva samples were then taken, followed by the second drink. Thirty minutes after finishing the second drink, participants again completed the task battery twice (i.e., another hour of continuous testing). Before leaving, participants were required to provide a final saliva sample.

Computerised task battery

Visual analogue mood scales Mood was assessed at the start and end of the task battery using 18 visual analogue mood scales (after Herbert *et al.*, 1976). Each of these bipolar scales consisted of a pair of adjectives, e.g., drowsy – alert or happy – sad. Participants were instructed to move the cursor from a central position anywhere along the horizontal rule, towards either extreme of the scale, until the cursor was at a position representative of their mood at that time. The 18 scales were presented successively. Three mood factors were derived from the scales: alertness, anxiety and hedonic tone.

Focused attention task This choice reaction time task, developed by Broadbent *et al.* (1986, 1989), measures various aspects of selective attention. In this task target letters appeared in uppercase As and Bs in the centre of the screen. Participants were required to respond to the target letter presented in the centre of the screen, ignoring any distracters presented in the periphery, as quickly and as accurately as possible. The correct response to A was to press a key with the forefinger of the left hand while the correct response to B was to press a different key with the forefinger of the right hand. Prior to each target presentation three warning crosses were presented on the screen, the outside crosses were separated from the middle one by either 1.02 or 2.60 degrees. The crosses were on the screen for 500 ms and were then replaced by the target letter. The central letter was either accompanied by (i) nothing, (ii) asterisks, (iii) letters which were the same as the target or (iv) letters which differed from the target. The two distracters were always identical and the targets and accompanying letters were always A or B.

Participants were given ten practice trials followed by five blocks of 64 trials. In each block there were equal numbers of near and far conditions, A or B responses, and equal numbers of the four distracter conditions. The nature of the previous trial was controlled. This task lasted approximately 5 minutes. Caffeine has been shown to improve mean reaction, decrease lapses of attention (number of long responses $>$800 ms), and improve speed of encoding (differences in reaction time between conditions when the target was alternated from the previous trial and when the target was repeated from the previous trial).

Categoric search task This task was also developed by Broadbent *et al.* (1986, 1989) and is similar to the focused attention task previously outlined. Each trial started with the appearance of two crosses in the positions occupied by the non-targets in the focused attention task (i.e., 2.04 or 5.20 degrees apart). The target letter then appeared in place of one of these crosses. However, in this task participants did not know in which location (right or left) the target would appear. On half the trials the target letter A or B was presented alone and on the other half it was accompanied by a distracter, in this task a digit (1–7). Again the number of near and far stimuli, A vs. B responses, and digit or blank conditions were controlled. Half of the trials led to compatible responses (i.e., the letter A on the left side of the screen, or the letter B on the right) whereas the others were incompatible. The nature of the preceding trial was also controlled. In other respects (practice, number of trials, etc.) the task was identical to the focused attention task. This task also lasted approximately 5 minutes. As in the focused attention task, caffeine has been shown to improve mean reaction, decrease lapses of attention (number of long responses $>$1000 ms) and improve speed of encoding (differences in reaction time between conditions when the target was alternated from the previous trial and when the target was repeated from the previous trial).

Variable fore-period simple reaction time task In this task a box was displayed in the centre of the screen and at varying intervals (from 1–8 seconds) a target square would appear in the box. As soon as they detected the square, participants were required to press a response key using the forefinger of their dominant hand only. This task lasted for approximately 5 minutes. Caffeine has been shown to improve overall mean reaction time.

Repeated digits vigilance task This visual cognitive vigilance task measures the ability to detect targets at irregular intervals. Participants were shown successive presentations of three digit numbers (e.g., 473) in the centre of the screen at the rate of 100 per minute. Each three-digit number usually differed from the one immediately preceding it, with one out of the three digits being replaced with a different digit (e.g., 463, 563, 562). Occasionally (8 times a minute) the same three-digit number was presented on successive trials. Participants were instructed to detect these repetitions and respond as quickly as possible by pressing a response key using the forefinger of their dominant hand. The task lasted for 5 minutes. Previous research has shown caffeine to improve mean response time to targets and/or the total number of hits (correct detection of a repeat).

Measurement of caffeine consumption Each participant completed a questionnaire recording the type of drinks generally consumed on a daily basis. From this a measure of daily caffeine consumption was derived (using values from Barone and Roberts, 1996). In addition, saliva assays were taken at baseline in order to verify self-reported measures of consumption.

Statistical analysis Following description of the consumption of caffeine, the main analyses are concerned with the effects seen after the first drink (Time 1) and at the last test (after two drinks). Analyses of co-variance, with the baseline data as covariates, were carried out on the Time 1 and Time 4 data. The analysis of the Time 1 data compared caffeine and placebo conditions. Analyses of the Time 4 data compared placebo/placebo, caffeine/placebo and caffeine/caffeine conditions. Order of conditions was included as a between subject factor in the analyses.

Results

Prior consumption of caffeine

The consumption diary showed that consumption was consistent across the day prior to each condition (Placebo/Placebo: mean caffeine ingestion = 115.6 mg, s.e. = 12.8; Caffeine/Placebo: mean caffeine ingestion = 102.4 mg, s.e. = 12.4; Caffeine/Caffeine: mean caffeine ingestion = 104.8 mg, s.e. = 11.6). This was confirmed by the saliva levels at baseline (Placebo/Placebo: mean = 4.31, s.e. = 0.68 μg/ml; Caffeine/Placebo: mean = 3.84, s.e. = 0.54 μg/ml; Caffeine/Caffeine: mean = 3.82, s.e. = 0.40 μg/ml). Neither subjective reports of consumption nor saliva levels differed significantly across conditions.

Effects of the caffeine manipulation on saliva levels of caffeine

The first dose of caffeine significantly increased saliva levels of caffeine measured at the end of the second test battery (Placebo/Placebo: mean = 4.02, s.e. = 0.64 μg/ml; Caffeine/Placebo: mean = 6.47, s.e. = 0.65 μg/ml; Caffeine/Caffeine: mean = 6.98, s.e. = 0.67 μg/ml). Similarly, the second dose of caffeine also led to an increase in saliva caffeine levels (Placebo/Placebo: mean = 3.35, s.e. = 0.54 μg/ml; Caffeine/Placebo: mean = 6.28, s.e. = 0.73 μg/ml; Caffeine/Caffeine: mean = 9.73, s.e. = 0.95 μg/ml).

Baseline data

Analyses of variance showed no significant differences between baseline data for the three conditions.

The effect of fatigue

The effects of fatigue can be seen by looking at how task performance changes over the test sessions in the condition where both drinks contained placebo (PP). On the whole, there were the expected negative effects of prolonged testing and decreasing circadian alertness on both mood and performance measures (see Table 1).

In the following two sections only significant effects will be reported. However, Table 1 provides group means for all tasks.

Effects of caffeine in alert individuals

The pattern of results at Test 1 was directly comparable to those obtained by Christopher *et al.* (2005). They found caffeine to significantly improve vigilance performance and the speed of encoding new information; ratings of alertness also improved with caffeine. The present study again showed that caffeine significantly improved speed of encoding (focused attention task – $F(1,53) = 4.42$, $p < 0.05$) and vigilance performance (hit rate – $F(1,53) = 8.63$, $p < 0.01$). It also increased ratings of alertness at the end of the test battery ($F(1,53) = 6.53$, $p < 0.05$).

Effects of caffeine in fatigued individuals

This section describes the effects of caffeine on fatigued volunteers (Test 4 scores, Table 1). It also compares the effect of a single dose of caffeine with the effects of two consecutive doses. Where the term 'linear dose-response' is used the statistic reported is the linear component from the ANCOVA. The effect of caffeine on speed of encoding new information in the focused attention task was no longer significant at Time 4, although numerically both caffeine conditions showed faster encoding of new information. However, the total number of repeats detected correctly (repeated digits task) still showed a significant effect of caffeine ($F(2,107) = 3.35$, $p < 0.05$). What was also evident was a linear dose-response effect of caffeine on mean reaction time for two tasks, namely the categoric search task ($F(1,53) = 4.91$, $p < 0.05$) and the simple reaction time task ($F(1,53) = 16.48$, $p < 0.001$; Fig. 1). The frequency with which attentional lapses occurred (long responses – categoric search task) also decreased as a function of caffeine dose ($F(1,53) = 8.25$, $p < 0.01$; Fig. 2). For alertness ratings, there was also a linear dose-response effect of caffeine at both the start of the final test battery ($F(1,53) = 10.71$, $p < 0.01$) and at the end ($F(1,53) = 8.79$, $p < 0.01$).

Discussion

In a previous study (Christopher *et al.*, 2005) we reported improvements in cognitive performance and self-reported mood following caffeine ingestion in non-fatigued volunteers who had previously been consuming caffeinated beverages during the day. In that study, caffeine was found to increase subjective ratings of alertness, increase the speed of processing new information and improve vigilance task performance. As predicted, these effects were also found in the present study when volunteers were relatively non-fatigued (i.e., at the start of the test session).

Furthermore, the present study demonstrated additional effects of caffeine in volunteers who had been fatigued by prolonged testing (i.e., effects only seen towards the end of the test session): faster simple reaction time (SRT) and fewer long responses (i.e., attentional lapses) in choice reaction time tasks. Increases in SRT and the occurrence of long responses are clear indications of increasing fatigue, thought to reflect depleted levels of central NA (e.g., Smith *et al.*, 2003); caffeine's ability to counteract these effects has important applications in real-life performance (e.g., driving: Horne and Reyner, 1996; Brice and Smith, 2001).

Table 1 Adjusted means for all tasks across all conditions (Time 1 = first post-drink test; P = placebo; C = caffeine; Time 4 = last test; pp = placebo in both drinks; CP = caffeine in first drink, placebo in second; CC = caffeine in both drinks)

Task	Variable	Time 1 adjusted means	Standard error in means	ANCOVA	Time 4 adjusted means	Standard error in means	ANCOVA
Mood (at start)	Alertness (high scores = greater alertness)	P = 230 C = 235	5.94 6.90	$F(1,53) = 1.17$, $p = 0.29$	PP = 195 CP = 211 CC = 215	6.31 6.40 6.01	$F(2,107) = 5.86$, $p = 0.004$**
Focused attention	Mean reaction time (ms)	P = 376 C = 371	4.37 5.46	$F(1,53) = 0.14$, $p = 0.71$	PP = 375 CP = 373 CC = 372	5.30 5.69 5.03	$F(2,107) = 0.05$, $p = 0.94$
	Number of lapses of attention	P = 1.63 C = 1.38	0.37 0.25	$F(1,53) = 0.60$, $p = 0.44$	PP = 1.95 CP = 2.05 CC = 1.60	0.49 0.59 0.32	$F(2,107) = 0.22$, $p = 0.81$
	Speed of encoding (ms)	P = 23.2 C = 18.8	3.33 2.65	$F(1,53) = 4.42$, $p = 0.04$*	PP = 16.4 CP = 11.8 CC = 12.9	3.31 3.06 3.19	$F(2,107) = 2.23$, $p = 0.11$
Categoric search	Mean reaction time (ms)	P = 484 C = 478	5.98 7.75	$F(1,53) = 0.45$, $p = 0.51$	PP = 487 CP = 473 CC = 471	6.70 7.37 6.33	$F(2,107) = 3.53$, $p = 0.03$*
	Number of lapses of attention	P = 2.68 C = 2.62	0.54 0.48	$F(1,53) = 0.01$, $p = 0.91$	PP = 3.55 CP = 2.62 CC = 1.91	0.73 0.51 0.29	$F(2,107) = 5.43$, $p = 0.006$**
	Speed of encoding (ms)	P = 12.7 C = 10.9	4.07 3.00	$F(1,53) = 1.00$, $p = 0.32$	PP = 12.9 CP = 11.8 CC = 11.3	3.39 3.45 4.10	$F(2,107) = 0.27$, $p = 0.76$
Simple reaction time	Mean reaction time (ms)	P = 347 C = 342	9.46 7.62	$F(1,53) = 2.80$, $p = 0.10$	PP = 366 CP = 353 CC = 343	10.10 8.01 8.05	$F(2,107) = 8.30$, $p = 0.0004$**
Repeated digits	Mean reaction time (ms)	P = 694 C = 680	12.9 12.5	$F(1,53) = 1.76$, $p = 0.19$	PP = 687 CP = 676 CC = 672	12.7 12.00 11.50	$F(2,107) = 1.54$, $p = 0.22$
	Total number of hits	P = 28.7 C = 30.1	0.89 0.93	$F(1,53) = 8.63$, $p = 0.005$**	PP = 28.4 CP = 29.9 CC = 30.0	1.05 0.98 0.81	$F(2,107) = 3.35$, $p = 0.04$*
Mood (at end)	Alertness (high scores = greater alertness)	P = 203 C = 209	6.08 7.40	$F(1,53) = 6.53$, $p = 0.01$**	PP = 192 CP = 202 CC = 207	6.66 6.85 5.89	$F(2,107) = 3.88$, $p = 0.02$*

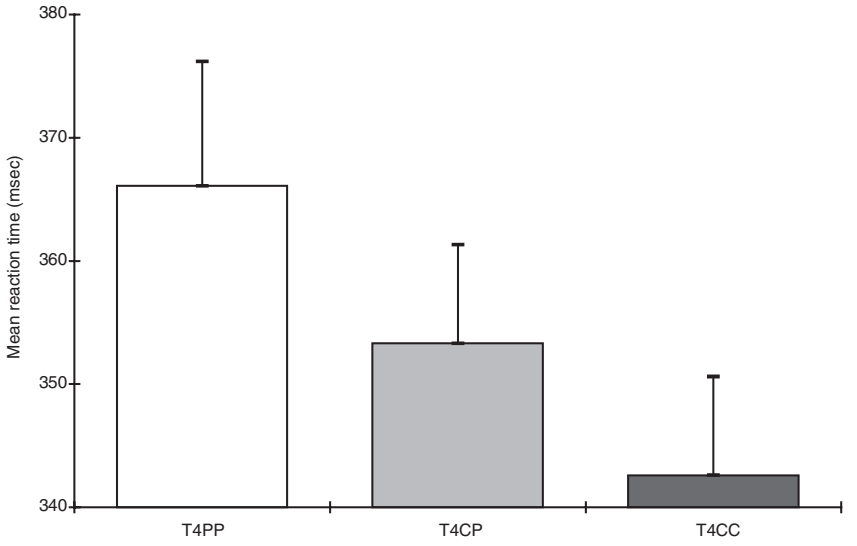

Figure 1 Mean reaction time in the simple reaction time task at Test 4 for each caffeine condition (PP = placebo in both drinks; CP = caffeine in first drink, placebo in second; CC = caffeine in both drinks; scores are the adjusted means from the ANCOVA, s.e.s shown as bars; lower scores = faster reaction time)

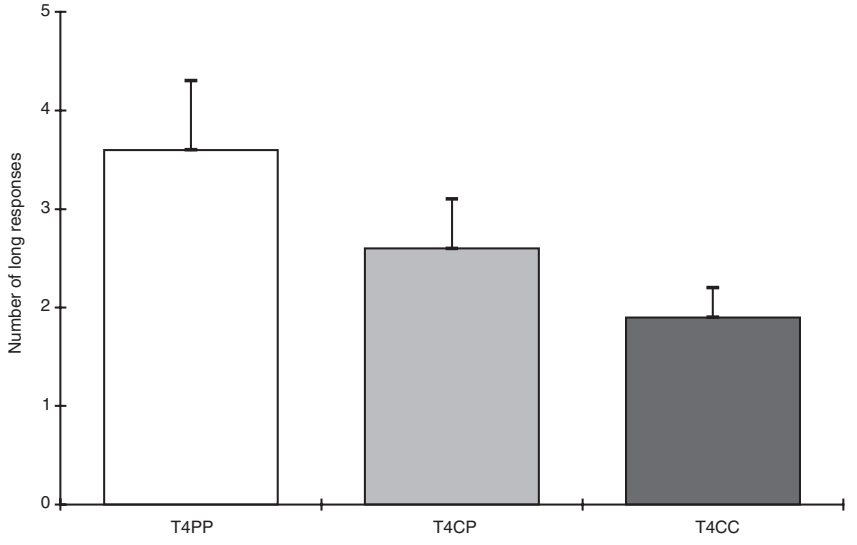

Figure 2 Number of long responses (>1000 ms) in the categoric search task at Test 4 for each caffeine condition (PP = placebo in both drinks; CP = caffeine in first drink, placebo in second; CC = caffeine in both drinks; scores are the adjusted means from the ANCOVA, s.e.s shown as bars; lower scores = fewer lapses of attention)

A recent study of effects of caffeine after 4, 6 or 8 hours caffeine abstinence only found effects in the group who had abstained for 8 hours (Heatherley *et al*., 2005). This study differs in a number of ways from the present one (e.g. task battery; method of analysis, no measure of saliva caffeine as an indicator of prior consumption). Indeed, none of the performance variables that showed effects here at the first post-drink test were included in the study by Heatherley *et al*., (2005). Furthermore, they found effects of caffeine in the 8 hour abstinence group for variables that have been shown to be generally insensitive to caffeine even in overnight deprived volunteers (e.g. delayed recall; the Eriksen effect).

We also found linear dose-response relationships for caffeine on a number of mood and performance measures (self-reported alertness, SRT and mean RT and the number of long responses in the categoric search task). These linear dose responses contrast with the flat dose-response relationships reported by Robelin and Rogers (1998) and Yeomans *et al.* (2002).

There are other potentially important methodological differences between these previous studies and the present one. For example, the performance task battery employed here is likely to be more cognitively demanding than the tasks used by Robelin and Rogers (a 1 minute finger-tapping task followed by a 20–25 minute simple reaction time task) or Yeomans *et al.* (10-minute vigilance task only). As was indicated earlier, previous studies have shown that the underlying level of fatigue or arousal is an important factor in demonstrating the effects of caffeine on cognitive and psychomotor tasks. Therefore, it is likely that the long

duration, fatigue-inducing test sessions (carried out at times when circadian arousal levels are naturally decreasing) used in this study also increased the likelihood of finding caffeine effects.

In summary, this study has replicated our previous demonstration of improvements in mood and cognitive performance following caffeine ingestion in consumers who have not abstained from caffeine for a long period. It has also demonstrated linear dose-response relationship for caffeine, a finding which further undermines the view that caffeine's effects are largely due to the removal of withdrawal effects (e.g., James, 1994; Rogers *et al.*, 2003). Finally, we have shown how the effects of caffeine differ in volunteers when they are fatigued compared to when they are relatively alert, which is consistent with results from recent studies of caffeine and different neurotransmitters (e.g., Smith *et al.*, 2003).

The research reported here was part of a project that addressed the issue of caffeine withdrawal using a variety of methodologies (see Smith, 2004). One approach compared regular consumers and non-consumers. The results from this study confirmed those obtained by Haskell *et al*. (2005), namely that no effects of overnight withdrawal were observed and both non-consumers and withdrawn consumers showed a more positive mood and improved performance after caffeine. Another method examined effects of caffeine after a "washout" period of a week. The rationale behind this method is that any effects of withdrawal should have disappeared after "washout" and if the effects of caffeine reflect removal of effects of withdrawal then they should not be observed after "washout". The results showed effects of caffeine even in individuals who were withdrawn for a week. Overall, the present study and associated research suggest that one should consider alternative mechanisms underlying effects of caffeine on behaviour. Different types of effects of caffeine are observed in alert and fatigued volunteers. These may plausibly be accounted for by effects of caffeine on different neurotransmitter systems and human volunteer studies suggest that changes in the cholinergic and noradrenergic systems could underlie the different effects obtained here.

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