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ORIGINAL INVESTIGATION

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Cognitive and mood improvements of caffeine in habitual consumers and habitual non-consumers of caffeine

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Abstract *Rationale:* The cognitive and mood effects of caffeine are well documented. However, the majority of studies in this area involve caffeine-deprived, habitual caffeine users. It is therefore unclear whether any beneficial findings are due to the positive effects of caffeine or to the alleviation of caffeine withdrawal. *Objectives:* The present placebo-controlled, double-blind, balanced crossover study investigated the acute cognitive and mood effects of caffeine in habitual users and habitual non-users of caffeine. *Method:* Following overnight caffeine withdrawal, 24 habitual caffeine consumers (mean=217 mg/day) and 24 habitual non-consumers (20 mg/day) received a 150 ml drink containing either 75 or 150 mg of caffeine or a matching placebo, at intervals of ≥48 h. Cognitive and mood assessments were undertaken at baseline and 30 min post-drink. These included the Cognitive Drug Research computerised test battery, two serial subtraction tasks, a sentence verification task and subjective visual analogue mood scales. *Results:* There were no baseline differences between the groups' mood or performance. Following caffeine, there were significant improvements in simple reaction time, digit vigilance reaction time, numeric working memory reaction time and sentence verification accuracy, irrespective of group. Self-rated mental fatigue was reduced and ratings of alertness were significantly improved by caffeine independent of group. There were also group effects for rapid visual information processing false alarms and spatial memory accuracy with habitual consumers outperforming non-consumers. There was a single significant interaction of group and treatment effects on jittery ratings. Separate analyses of each groups' responses to caffeine revealed overlapping but differential responses to caffeine. Caffeine tended to benefit consumers' mood more while improving performance more in the non-consumers. *Conclusions:* These results do not support a withdrawal alleviation model. Differences in the patterns of responses to caffeine by habitual consumers and habitual non-consumers may go some way to explaining why some individuals become caffeine consumers.

Keywords Caffeine · Withdrawal · Cognition · Mood · Performance · Consumers · Non-consumers

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Introduction

The most commonly reported experimental effects of caffeine are increases in ratings of alertness (Rogers et al. 2003; Quinlan et al. 2000) and improvements in measures of reaction time and vigilance (Smit and Rogers 2000; Lieberman et al. 1987; Richardson et al. 1995). However, even on these measures there is contradiction in the literature, with some studies reporting no effects of caffeine (Loke and Meliska 1984) and others finding positive effects only in certain groups (e.g. the elderly; Swift and Tiplady 1988) or in certain situations (e.g. low arousal, or under the influence of a depressant; Reyner and Horne 2000; Mackay et al. 2002; Smith et al. 2003). There are also reports of positive effects of caffeine on information processing, memory and logical reasoning (Smith et al. 1994; Smit and Rogers 2000; Warburton et al. 2001). Whilst there is less support for these latter findings, there is also little evidence to suggest that caffeine produces any impairment to performance, at least at typical everyday levels.

The reason for this lack of consistency in the literature can largely be attributed to methodological issues. For instance, there is large variability between studies in the doses of caffeine administered, with some using single acute doses equivalent to over fivefold the amount found in the average cup of coffee (Kaplan et al. 1997). This should be viewed in the context of reports of positive

effects from doses of caffeine as low as 12.5 mg (Smit and Rogers 2000). There are also wide differences in the periods of caffeine abstention prior to testing, with these ranging from 1 h (e.g. Warburton et al. 2001) to up to 3 weeks (e.g. Heatherley et al. 2004).

One recurrent theme in the literature on the behavioural and subjective effects of caffeine concerns the issue of whether caffeine produces any net benefits, or whether its effects merely represent an alleviation of withdrawal (James 1994; Rogers and Dernoncourt 1998). The issue of withdrawal in relation to the effects of caffeine stems from the large number of studies which have employed habitual caffeine consumers who have abstained from caffeine overnight for the purposes of the research. The most commonly reported symptoms of caffeine withdrawal in clude headache, drowsiness and lethargy, and decreased energy and concentration (Phillips-Bute and Lane 1998). It has also been reported that caffeine withdrawal can lead to impaired performance on vigilance tasks (Lane and Phillips-Bute 1998). These findings have led to the suggestion that participants who have abstained from caffeine are performing at sub-normal levels and that the administration of caffeine merely restores performance to normal levels.

Several methods have been employed in order to gauge whether improvements in mood and performance following administration of caffeine are evident without the confounding effect of withdrawal. These have included pre-dosing participants with a standard amount of caffeine, allowing *ad libitum* caffeine consumption prior to testing, or withdrawing caffeine consumers from caffeine for a period of a week or more. All three methods present problems. Pre-loading with a standard dose of caffeine does not account for the different doses needed to alleviate withdrawal in different participants. On the other hand, *ad libitum* consumption is confounded by individual differences in patterns of daily consumption raising the possibility that participants are at different levels of caffeine withdrawal prior to treatment. "Washing out" caffeine consumers to levels where they no longer show any withdrawal effects presents possibly the best method of assessing positive effects of caffeine. Nevertheless, the method is difficult in practical terms in that it necessitates a high level of compliance (or constant monitoring of dietary habits), including substitution of caffeinated products with decaffeinated equivalents.

An alternative method for measuring the absolute effects of caffeine is to compare its effects in overnight withdrawn consumers with those in habitual non-consumers (who are clearly not withdrawn). This approach is not without its own attendant problems, most notably that non-consumers are rare, and may be considered as self-selecting (possibly due to an inherent caffeine insensitivity or hypersensitivity). Nevertheless, if withdrawn caffeine consumers' performance is significantly lower than that of non-consumers, and drinking caffeine simply reverses this deficit, this would offer strong support for a withdrawal alleviation model. If, on the other hand, such differences are not evident in the absence of caffeine, and both groups benefit to a similar extent from a caffeine dose, this would provide evidence in favour of caffeine imparting absolute benefits on performance.

Comparisons of non-consumers' and consumers' baseline scores have shown detrimental effects of caffeine withdrawal on consumers' mood but not performance (Rogers et al. 2003). It is possible that these differences between consumers and non-consumers reflect expectancy rather than actual effects in this case, as the consumers were asked to abstain from caffeine prior to testing. Previous comparisons of the above two groups' responses to caffeine have produced significant effects on mood. Richardson et al. (1995) found that caffeine influenced ratings of headache, tiredness and jitteriness, irrespective of group. Rogers et al. (2003) also found that caffeine significantly increased ratings of alertness in both consumers and non-consumers of caffeine. Using comparisons of habitual consumers and non-consumers has therefore generated equivocal results regarding caffeine's mood effects. Moreover, these studies have been limited as to the memory and cognitive measures employed.

The aim of the present study was therefore to conduct a systematic assessment both of the behavioural effects of two doses of caffeine and the contribution to these effects of caffeine withdrawal. This placebo-controlled, double-blind, balanced crossover study examined the effects of caffeine on mood and on the performance of a comprehensive range of tasks known to be sensitive to caffeine. These included a subset of tests from the Cognitive Drug Research (CDR) computerised test battery. The CDR battery also contained tasks with no known sensitivity to caffeine. This was in order to produce a cognitive profile for caffeine thus allowing meaningful comparison with other drugs. Mood and performance were assessed in acutely (overnight) withdrawn habitual consumers and habitual non-consumers of caffeine. As outlined above, individuals who completely forgo caffeine may do so because of abnormal sensitivity to the drug. For this reason in the present study we selected individuals who consumed very low levels of caffeine exclusively from products other than tea and coffee. Additionally, we assessed the behavioural effects of caffeine administered at typical everyday doses.

Materials and methods

Initial screening

Participants were initially recruited from a database of potential volunteers on the basis of their self-reported caffeine consumption. Potential volunteers were then asked to complete a questionnaire which assessed average caffeine consumption on the basis of their responses to questions regarding daily consumption of tea, coffee, cocoa and caffeinated soft drinks. For the purposes of the study, 'habitual non-consumers' were defined as those who refrained from drinking tea or coffee and who consumed less than 50 mg/day of caffeine from other sources (primarily soft drinks) their mean consumption

was 20 mg caffeine/day (range 0–47 mg). Consumers were defined as those who consumed tea and/or coffee and consumed more than 50 mg caffeine/day (mean consumption 217 mg/day, range 60–800 mg). Prior to participation in the study volunteers signed an informed consent form and completed a medical health questionnaire. Only those participants who reported being in good health and who were taking no medication, other than the contraceptive pill, were included in the study. Habitual smokers were excluded from the study. All participants abstained from caffeine and alcohol for a minimum of 12 h prior to the first-testing session of the morning.

Participants

Twenty-nine males and 19 females (mean age 23.4 years, range 18–46 years) took part in the study, which was approved by the Northumbria University Division of Psychology Ethics Committee. The participants comprised two groups of 24 habitual consumers (seven female and 17 male, mean age 23.8 years, range 19–46 years) and 24 habitual non-consumers of caffeine (12 female and 12 male, mean age 22.9 years, range 18–33 years). The groups did not differ in terms of age ($t(46)=0.592$, $p=0.555$) nor gender composition ($\chi^2_{(1)}=2.178$, $p=0.14$).

Salivary caffeine levels

Saliva samples were obtained by asking participants to expectorate into a tube. Samples were taken immediately prior to baseline assessment in order to confirm compliance to overnight abstinence and immediately prior to post-treatment assessment to confirm effective caffeine absorption. The saliva samples were immediately frozen at −20°C until thawing for batch analysis using the Emit system (Syva, Palo Alto, USA). This is an enzyme immunoassay intended to measure caffeine as a metabolite and is based on competition for antibody binding sites between caffeine and an enzyme-labelled drug.

Cognitive and mood measures

CDR assessment battery

A tailored version of the Cognitive Drug Research battery (CDR Ltd, Goring-on-Thames, UK) was used (see Table 1). The CDR computerised assessment battery has been used in hundreds of European and North American drug trials, and has been shown to be sensitive to acute cognitive improvements as well as impairments with a wide variety of substances (e.g. Moss et al. 1998; Scholey et al. 1999; Kennedy et al. 2002, 2003). The selection of computer-controlled tasks from the system was administered with parallel forms of the tests being presented at each testing session. Presentation was via laptop computers. All responses were recorded via two-button (YES/NO) response boxes with the exception of the written tasks which were word recall and digit symbol substitution (DSST), and the tracking task, which involved the use of a joystick. For a full description of the tasks used, including the DSST (Weschler 1958); see Scholey and Kennedy (2004). Additionally, a rapid visual information processing task was included (see Kennedy et al. 2003), along with a tracking task and a logical reasoning task (see below).

Tracking A box appeared on the screen which participants could move in two dimensions using a joystick. Participants were required to use the joystick to make the box follow a randomly moving cross as closely as they could. Task performance was measured as average distance from target (mm). The task lasted for 1 min.

Logical reasoning A series of statements referring to the relationships between two letters appeared on the screen one at a time (e.g. “a precedes b: ba”). Participants were required to decide if each statement correctly described the order of the two letters that followed it by pressing the ‘YES’ or the ‘NO’ button. Task measures were accuracy (%) and reaction time (ms).

Other cognitive measures

Sentence verification task Participants were shown a series of sentences and had to decide whether they were true (e.g. forks are manufactured goods) or false (e.g. dogs have wings). Thirty stimuli were presented and performance was measured as number correct and mean reaction time (ms).

Serial subtraction tasks: serial sevens Computerised versions of the serial subtraction tasks were implemented using tests of 2-min duration. Participants were required to count backwards from a given number as quickly and as accurately as possible using the number keys to enter each response. A random starting number between 800 and 999 was presented on the computer screen, which was cleared by the entry of the first response. The task was scored for total number of subtractions and number correct. In the case of incorrect responses, subsequent responses were scored as positive if they were scored as correct in relation to the new number.

Serial threes This was identical to the serial sevens task except that it involved serial subtraction of threes.

Subjective mood measures

Bond–Lader visual analogue scales (Bond and Lader 1974) Scores from the 16 Bond–Lader visual analogue scales were combined as recommended by the authors to form three mood factors: alert, calm and content.

Caffeine research visual analogue scales A further seven visual analogue scales (“relaxed,” “alert,” “jittery,” “tired,”

Table 1 Mean (±SEM) scores for all CDR outcome measures

		Consumers		Non-consumers	
		Baseline	Change from baseline	Baseline	Change from baseline
Immediate word recall (number correct)	Placebo	7.60±0.64	−0.54±0.42	6.42±0.45	−0.04±0.37
	75 mg	7.77±0.62	−1.21±0.28	6.56±0.38	−0.69±0.38
	150 mg	7.21±0.45	−0.19±0.42	6.33±0.47	0.40±0.45
Simple reaction time (ms)[T]	Placebo	285±11.0	26.3±5.36	288±6.64	27.3±5.46
	75 mg	284±9.51	9.22±4.57	282±5.55	14.8±4.93
	150 mg	285±10.2	9.66±8.47	279±6.66	21.7±5.81
Digit vigilance accuracy (%)	Placebo	94.5±1.71	−0.09±1.47	95.9±0.98	−2.68±0.85
	75 mg	95.3±1.44	−1.02±0.71	96.3±0.76	−2.22±1.35
	150 mg	95.5±1.35	−0.83±0.96	96.1±0.81	0.56±0.62**
Digit vigilance reaction time (ms)[T]	Placebo	425±7.64	29.8±6.14	427±7.70	31.4±4.87
	75 mg	422±9.76	26.2±6.67	430±8.12	11.5±7.27*
	150 mg	428±8.45	15.9±5.19	416±7.30	15.2±5.25*
Choice reaction time accuracy (%)	Placebo	94.8±0.72	−0.83±0.75	95.1±0.54	0.33±0.61
	75 mg	95.3±0.84	1.25±0.99	95.6±0.58	1.17±0.68
	150 mg	94.4±0.74	0.50±0.65	95.5±0.59	0.58±0.73
Choice reaction time (ms)	Placebo	418±13.2	13.0±9.66	437±10.6	14.7±7.75
	75 mg	424±14.4	15.3±9.97	436±8.29	13.1±6.72
	150 mg	423±13.4	14.0±10.4	424±7.90	22.0±8.56
RVIP accuracy (%)	Placebo	65.0±4.90	−2.72±2.63	63.4±4.68	1.56±2.36
	75 mg	63.3±4.01	7.88±2.53**	66.0±5.26	0.78±2.30
	150 mg	63.3±4.15	4.62±3.41	65.9±4.26	4.17±2.68
RVIP reaction time (ms)	Placebo	478±14.9	14.1±11.5	488±17.7	20.7±11.4
	75 mg	488±20.3	−13.4±13.6	479±13.6	0.25±10.6
	150 mg	480±16.3	3.27±11.9	485±13.3	−8.39±11.1
RVIP false alarms (number)[G]	Placebo	1.13±0.34	−0.22±0.23	1.42±0.48	0.46±0.57
	75 mg	1.09±0.29	−0.39±0.36	0.83±0.20	1.00±0.35
	150 mg	1.39±0.78	−0.04±0.15	1.46±0.30	0.25±0.47
Tracking (mm)	Placebo	22.7±0.62	−0.73±0.55	25.7±2.58	−2.52±2.63
	75 mg	22.9±0.76	−1.12±0.60	23.0±0.64	−1.45±0.50
	150 mg	22.8±0.62	−1.18±0.62	24.3±2.01	−2.06±1.92
Spatial memory (sensitivity index)[G]	Placebo	0.91±0.02	0.04±0.02	0.94±0.01	−0.02±0.02
	75 mg	0.89±0.03	0.06±0.03	0.96±0.01	−0.02±0.02
	150 mg	0.95±0.01	−0.01±0.01	0.95±0.01	−0.01±0.01
Spatial memory reaction time (ms)	Placebo	568±31.7	−52.7±15.1	591±33.1	−55.8±24.8
	75 mg	568±28.7	−69.7±9.26	568±19.7	−57.2±9.83
	150 mg	562±22.9	−41.0±15.1	570±19.8	−38.6±13.9
Logical reasoning accuracy (%)	Placebo	88.9±2.48	−1.21±1.97	81.9±4.48	−2.43±1.58
	75 mg	90.1±2.65	−0.17±1.16	80.0±4.34	1.04±1.49
	150 mg	88.9±2.21	0.87±1.53	82.8±4.18	−4.69±1.81
Logical reasoning reaction time (ms)	Placebo	2,969±187	−289±123	2,930±199	117±179
	75 mg	2,882±183	−198±112	2,937±244	−180±164
	150 mg	2,964±217	−216±150	3,031±222	−86.1±97.4
Numeric working memory (sensitivity index)	Placebo	0.91±0.02	−0.01±0.02	0.91±0.00	0.01±0.02
	75 mg	0.88±0.02	0.03±0.01	0.93±0.01	0.00±0.01
	150 mg	0.90±0.02	0.00±0.01	0.91±0.02	0.02±0.01
Numeric working memory reaction time (ms)[T]	Placebo	583±22.7	−23.9±11.0	622±23.9	−2.28±11.3
	75 mg	591±26.5	−35.7±9.54	623±26.8	−23.7±12.7
	150 mg	604±27.7	−41.2±11.1	628±26.0	−44.7±11.2**
Digit symbol substitution (number)	Placebo	68.5±2.04	2.50±1.42	71.5±2.11	0.92±1.64
	75 mg	67.7±2.32	2.33±0.88	70.7±2.32	2.79±0.75
	150 mg	68.8±2.33	0.04±1.23	70.6±2.22	3.08±0.74

Table 1 (continued)

		Consumers		Non-consumers	
		Baseline	Change from baseline	Baseline	Change from baseline
Delayed word recall (number correct)	Placebo	4.46±0.55	−1.02±0.48	4.40±0.52	−1.56±0.53
	75 mg	4.96±0.51	−1.96±0.51	4.50±0.42	−1.96±0.51
	150 mg	4.85±0.53	−1.15±0.55	4.83±0.52	−1.88±0.52
Delayed word recognition (sensitivity index)	Placebo	0.61±0.04	−0.06±0.04	0.59±0.05	−0.02±0.05
	75 mg	0.62±0.04	−0.07±0.04	0.60±0.04	−0.04±0.04
	150 mg	0.62±0.04	−0.04±0.04	0.65±0.04	−0.05±0.05
Delayed word recognition reaction time (ms)	Placebo	721±30.2	−31.0±25.8	736±22.6	18.5±18.6
	75 mg	724±33.5	−30.5±25.8	705±17.1	14.0±20.0
	150 mg	715±18.7	−30.9±13.1	746±24.7	−1.30±21.3
Delayed picture recognition (sensitivity index)	Placebo	0.64±0.06	0.00±0.04	0.73±0.04	−0.11±0.05
	75 mg	0.68±0.05	−0.03±0.04	0.71±0.04	−0.08±0.05
	150 mg	0.66±0.05	−0.06±0.04	0.67±0.04	−0.01±0.05
Delayed picture recognition reaction time (ms)	Placebo	847±39.5	−51.9±37.3	873±25.6	−32.5±28.3
	75 mg	808±26.6	−2.22±13.0	841±24.5	−29.0±23.1
	150 mg	866±36.8	−44.1±26.8	831±19.9	39.3±17.9*

Baseline and change from baseline scores are presented for consumers and non-consumers. Scores presented in bold depict significant main effects from the primary analysis ANOVA ($p<0.05$).
T treatment effects, *G* group effects (consumers vs. non-consumers)
Significant effects from the secondary analysis' planned comparisons are represented by asterisk(s) indicating which group(s) were affected and by which treatment(s) (*$p<0.05$; **$p<0.01$).

"tense," "headache," "overall mood") that have previously been used in research into the effects of caffeine were also utilised (Rogers et al. 2003) with the addition of a single "mental fatigue" visual analogue scale which has been shown to be sensitive to a caffeine–glucose drink (Kennedy and Scholey 2004). Participants rated their current subjective status for each of the descriptors by making a mark on a 100-mm line with the end points labelled "not at all" (left hand end) and "extremely" (right hand end), with the exception of "overall mood" which was labelled "very bad" and "very good." Alert and tired ratings were combined (as previously recommended; Rogers et al. 2003) to give a composite "alertness" rating and tense and relaxed were combined to give a "tension" rating with more positive scores denoting greater alertness and more tension, respectively.

Treatments

Participants received three drinks containing 0 (placebo), 75 and 150 mg of caffeine hydrochloride BP (Merck, Darmstadt, Germany) on separate occasions. In each case the caffeine was presented in a 150-ml drink containing 30 ml of Robinsons Special R Apple and Blackcurrant Juice Drink with no added sugar (Robinsons Soft Drinks, Chelmsford, UK). Five minutes was allowed for drink consumption. There were several reasons for this choice of a juice drink over a more naturalistic caffeine vehicle. Firstly, tea and coffee and even hot water alone have been shown to have behavioural effects irrespective of caffeine content which could interfere with the findings (Quinlan et al. 2000). Secondly, there are obvious expectancy effects attached to tea and coffee which are likely to influence task outcomes and may differ between the two groups. Finally, many of the habitual non-consumers of caffeine did not drink coffee or tea because they disliked the taste.

Procedure

Each participant was required to attend a total of 4 study days that were conducted 48 h apart to ensure a sufficient wash out between conditions. Testing took place in a suite of laboratories with participants visually isolated from each other. On arrival at their first session on the first day, participants were randomly allocated to a treatment regime using a Latin square design which counterbalanced the order of treatments across the 3 active days of the study.

The first day involved completion of the test battery four times. This was undertaken in order to control for practice effects and to allow familiarisation with the test battery and procedure on subsequent visits. The practice day data were not included in any analyses.

Each of the 3 active study days comprised two identical testing sessions. The first was a pre-dose testing session, which established baseline performance for that day. This was immediately followed by drink consumption with the second assessment commencing 30 min post-drink.

Each testing session lasted ~30 min and comprised producing a saliva sample, completion of the CDR test battery, a sentence verification task, serial subtractions (threes and sevens) and visual analogue mood scales.

Statistics

Salivary caffeine levels were analysed to assess compliance to caffeine abstinence and effective caffeine absorption.

Prior to the primary statistical analysis, separate one-way, repeated measures ANOVAs of pre-dose baseline data were conducted to ascertain any chance baseline differences in performance prior to the treatments. To assess the possibility that caffeine withdrawal leads to mood and performance deficits, one-way ANOVAs were conducted to ascertain any group (consumers/non-consumers) effects in the absence of treatment.

Scores on the individual task outcomes were analysed as 'change from baseline' using SPSS.

Primary analysis of the data from each measure was undertaken utilising two-way ANOVA [group (consumers/non-consumers)×treatment (75 mg/150 mg/placebo)] with repeated measures on the latter factor. This analysis was followed by a priori planned comparisons of the effect of treatment, with individual comparisons being made between placebo and each of the two levels of caffeine treatment (75 and 150 mg) utilising *t*-tests with the MSError from an omnibus ANOVA as an error term (Keppel 1991). In the case of significant interaction effects post-hoc analysis was conducted utilising Bonferroni *t*-tests. To ensure the overall protection level, only those planned comparisons associated with measures that generated a significant main effect or interaction effect on the initial analysis are reported. Furthermore, all testing was two-tailed, comparisons were strictly planned prior to the study, were restricted to the number of conditions minus one at each time-point, and only probabilities associated with these pre-planned comparisons were calculated.

The analyses described in the preceding sections are adequate to detect withdrawal effects and to determine whether consumers and non-consumers are similarly susceptible to the effects of caffeine. However, to further explore the possibility of group differences in the responses of consumers and non-consumers, a secondary analysis of each separate consumption groups' scores was undertaken by one-way ANOVA (comparing treatments) with any differences between treatments analysed with a priori planned comparisons, as described above.

Results

Salivary caffeine levels

Due to factors outside of the experimenters' control, it was only possible to obtain full datasets for 30 participants (15 per group) and only these are included in the analysis. However, it should be emphasised that all 48 participants complied in giving each saliva sample. Baseline salivary caffeine levels confirmed compliance with overnight abstinence. The mean values were 0.50 μg/ml for consumers and 0.36 μg/ml for non-consumers (levels below 1 mg/ml have been reported for 24-h caffeine abstinence; Hughes et al. 1991). Analysis of post-treatment salivary caffeine levels reflected effective caffeine absorption in both groups [$F(2,56)=6.93$, $p=0.002$). Planned comparisons revealed significantly higher salivary caffeine levels in both groups following both 75 mg caffeine [$t(56)=2.48$, $p=0.016$] and 150 mg caffeine [$t(56)=3.64$, $p=0.001$]. There was no significant treatment×group interaction.

Baseline scores

Prior to analysis of change from baseline data, mean pre-dose baseline scores for all three conditions (placebo, 75 mg, 150 mg caffeine) for each outcome (individual CDR task scores, sentence verification scores, serial subtraction scores and mood scale scores) were subjected to a one-way, repeated-measures ANOVA. There were no significant differences on any of the measures.

Group (consumers/non-consumers) effects in the absence of treatment

Mean pre-dose baseline scores for each group (habitual consumers, habitual non-consumers) for each outcome were subjected to a one-way ANOVA to assess any cognitive or mood differences between the groups in the absence of caffeine. There were significant group differences on the serial sevens subtraction task [$F(1,44)=6.58$, $p=0.014$] and the serial threes subtraction task [$F(1,44)=6.40$, $p=0.015$] with habitual consumers performing more subtractions than habitual non-consumers. In order to further examine effects of caffeine withdrawal, controlling for possible 'withdrawal expectancy' effects in consumers, a comparison of placebo change from baseline scores for the two groups was also carried out. There was a significant group effect on ratings of jitteriness [$F(1,44)=7.51$, $p=0.009$] with non-consumers becoming more jittery following placebo than consumers.

Primary analysis

CDR assessment battery

Mean pre-dose baseline scores, and change from baseline scores for each condition on each outcome measure are presented in Table 1. Only significant main effects and/or interactions for each outcome measure are reported below. Significant differences on cognitive tasks are presented in Fig. 1.

Simple reaction time Performance of the simple reaction time task produced a significant main effect of treatment [$F(2,92)=4.32$, $p=0.016$]. Planned comparisons revealed significantly improved performance irrespective of group following the 75 mg dose of caffeine [$t(92)=2.61$, $p=0.011$] (see Fig. 1a).

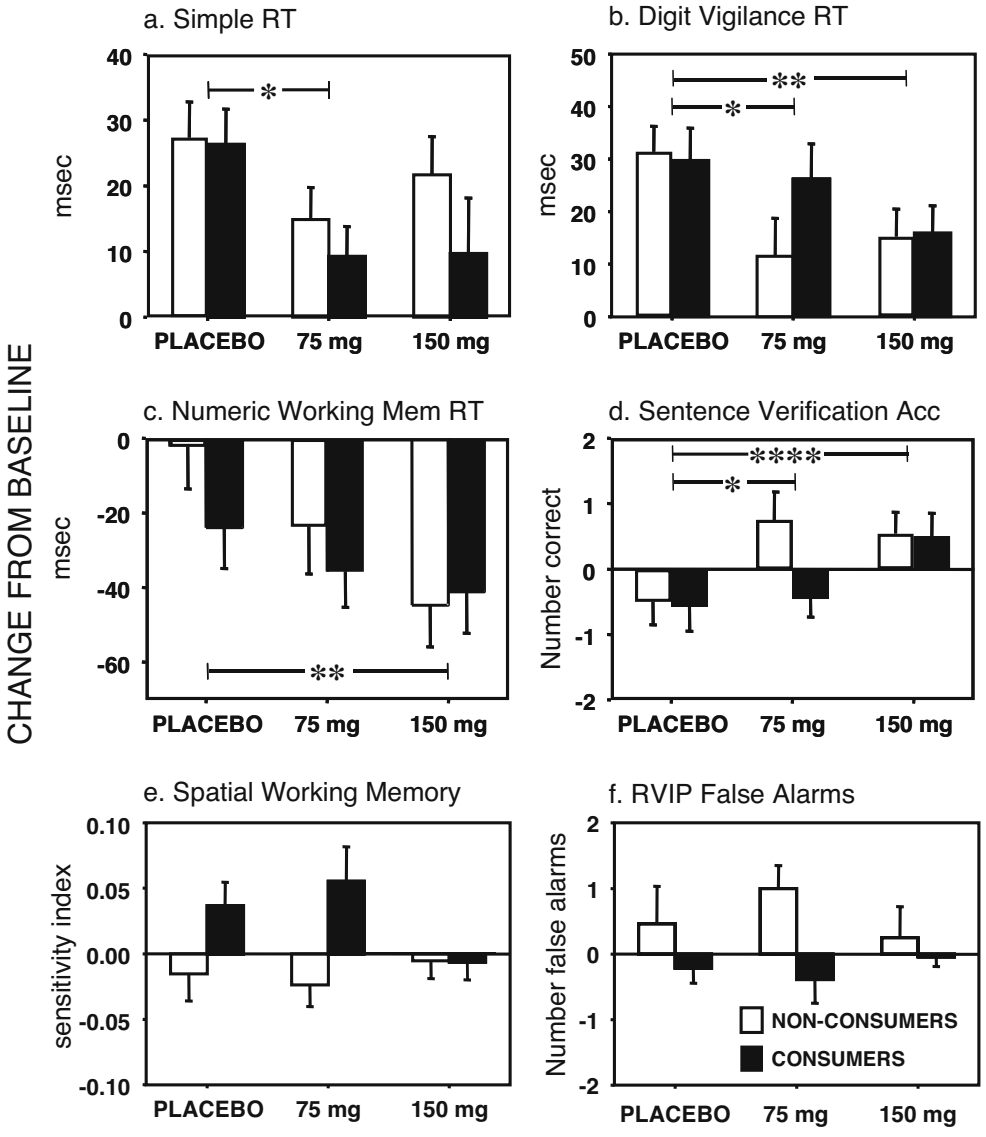

Fig. 1 Graphic representation of cognitive measures showing significant treatment effects, compared with placebo (**a**, **b**, **c**, **d**), and group effects (**e**, **f**). Means (±SEM) change from baseline scores are shown for consumers and non-consumers following placebo, and 75 and 150 mg caffeine (*p<0.05; **p<0.01; ****p<0.001)

Digit vigilance reaction time There was a significant treatment effect on digit vigilance reaction time [$F(2,92)$= 3.95, p=0.023]. Planned comparisons revealed that responses were significantly speeded up across groups following both the 75 mg [$t(92)$=2.09, p=0.040] and the 150-mg doses of caffeine [$t(92)$=2.67, p=0.009] (see Fig. 1b).

Numeric working memory reaction time There was a significant main effect of treatment on numeric working memory reaction time [$F(2,92)$=4.07, p=0.020]. Planned comparisons showed that 150 mg significantly improved performance irrespective of group [$t(92)$=2.85, p=0.005] (see Fig. 1c).

Spatial memory Whilst there was no effect of treatment overall there was a significant main effect of group (consumers/non-consumers) on the spatial memory task [$F(1,46)$=6.72, p=0.013; Fig. 1e]. Consumers outperformed non-consumers on this measure.

RVIP false alarms Data capture errors with one dataset resulted in only 47 scores being analysed for this task. There were significant group differences in the number of false alarms generated on the Rapid Visual Information Processing (RVIP) task [$F(1,45)$=5.64, p=0.022] with non-consumers producing more false alarms than consumers irrespective of treatment (Fig. 1f).

Other cognitive measures

Mean pre-dose baseline scores, and change from baseline scores for each condition on each outcome measure are presented in Table 2. Only significant main effects and/or interactions for each outcome measure are reported below.

Sentence verification accuracy Performance on the sentence verification task produced a significant main effect of treatment [$F(2,92)$=6.08, p=0.003]. Planned comparisons revealed that performance was significantly im-

Table 2 Mean (±SEM) scores for all non-CDR cognitive measures

		Consumers		Non-consumers	
		Baseline	Change from baseline	Baseline	Change from baseline
Sentence verification (number correct)[T]	Placebo	29.4±0.20	−0.58±0.37	28.9±0.32	−0.50±0.35
	75 mg	29.3±0.22	−0.46±0.28	28.3±0.58	0.75±0.43*
	150 mg	28.7±0.38	0.50±0.35**	28.3±0.43	0.54±0.33*
Sentence verification reaction time (ms)	Placebo	1.77±0.12	−0.27±0.07	1.74±0.10	−0.18±0.06
	75 mg	1.88±0.11	−0.31±0.08	1.83±0.16	−0.31±0.09
	150 mg	1.85±0.12	−0.31±0.06	1.69±0.10	−0.17±0.07
Serial threes subtraction (number)	Placebo	51.5±3.64	2.87±1.04	39.4±2.17	1.74±1.01
	75 mg	48.5±2.99	5.48±1.26	41.0±2.55	1.78±1.11
	150 mg	51.0±3.34	3.04±1.37	41.3±2.53	2.39±1.36
Serial threes subtraction (number correct)	Placebo	49.0±3.56	0.87±1.29	35.7±2.21	1.48±0.97
	75 mg	46.2±2.85	4.00±1.48	37.0±2.75	2.00±1.05
	150 mg	47.0±3.80	3.04±1.84	37.9±2.57	1.57±1.39
Serial sevens subtraction (number)	Placebo	32.8±2.47	1.57±1.12	24.4±1.86	0.22±1.35
	75 mg	32.1±2.41	2.39±0.76	25.0±2.39	−0.04±0.80
	150 mg	32.1±2.74	2.52±0.80	23.7±1.79	3.00±0.96
Serial sevens subtraction (number correct)	Placebo	29.3±2.45	1.22±1.19	21.1±2.07	−0.43±1.18
	75 mg	29.0±2.44	1.13±0.91	22.0±2.41	−0.17±0.95
	150 mg	28.6±2.81	1.70±0.93	20.6±1.89	2.04±1.09

Baseline and change from baseline scores are presented for consumers and non-consumers. Scores presented in bold depict significant main effects from the primary analysis ANOVA ($p<0.05$)

T treatment effects

Significant effects from the secondary analysis' planned comparisons are represented by asterisk(s) indicating which group(s) were affected and by which treatment(s) (*$p<0.05$; **$p<0.01$).

proved across groups following both the 75 mg [$t(92)=2.22$, $p=0.029$] and the 150 mg dose of caffeine [$t(92)=3.44$, $p=0.0009$] (see Fig. 1d).

Subjective mood measures

There were no significant effects on the Bond–Lader visual analogue scales. Mean pre-dose baseline scores as well as change from baseline scores for each condition on each outcome measure are presented in Table 3. There were a number of treatment effects on the caffeine research visual analogue scales (presented in Fig. 2). Due to data capture errors with two datasets it is only possible to report data for 46 participants.

Alertness Subjective ratings of alertness showed a main effect of treatment [$F(2,88)=3.52$, $p=0.034$]. Planned comparisons showed that alertness across groups significantly increased following both 75 mg [$t(88)=2.11$, $p=0.038$], and 150 mg of caffeine [$t(88)=2.27$, $p=0.029$] (see Fig. 2a).

Tired The effect of treatment upon alertness was largely due to effects on ratings of tiredness [$F(2,88)=4.56$, $p=0.013$]. Planned comparisons revealed that ratings of tiredness decreased following doses of 75 mg [$t(88)=2.16$, $p=0.033$] and 150 mg [$t(88)=2.67$, $p=0.009$] across both groups.

Mental fatigue There was also a main effect of treatment on ratings of mental fatigue [$F(2,88)=4.27$, $p=0.017$]. Planned comparisons revealed that mental fatigue was significantly decreased in both groups following the 75 mg dose [$t(88)=2.65$, $p=0.010$] and the 150-mg dose [$t(88)=2.37$, $p=0.020$] (Fig. 2b).

Jittery There was a significant interaction of group and treatment effects in ratings of jitteriness [$F(2,88)=4.83$, $p=0.010$]. Planned comparisons revealed that non-consumers were more jittery than consumers in the placebo condition [$t(88)=3.97$, $p=0.0001$] and were less jittery than consumers following 150 mg caffeine [$t(88)=2.25$, $p=0.027$] (Fig. 2c).

Secondary analysis

Secondary analyses were carried out separately on the scores from each of the groups.

Consumers

RVIP accuracy was significantly affected by treatment [$F(2,44)=3.99$, $p=0.026$]. Planned comparisons showed that this improvement was apparent following only the 75 mg dose [$t(44)=2.76$, $p=0.008$]. There was a significant main effect of treatment on sentence verification accuracy

Table 3 Mean (±SEM) scores for mood measures

			Consumers		Non-consumers	
			Baseline	Change from baseline	Baseline	Change from baseline
Bond–Lader factors	Alert	Placebo	54.0±3.75	−4.30±2.01	54.8±4.70	−7.11±3.98
		75 mg	52.8±3.60	3.37±2.85	53.2±4.05	1.21±4.44
		150 mg	54.3±3.39	0.79±4.29	55.3±4.28	1.28±4.16
	Content	Placebo	62.7±1.95	−2.27±1.87	65.1±3.56	−4.82±2.61
		75 mg	62.6±2.85	−1.02±1.34	64.4±3.99	−4.13±1.87
		150 mg	62.2±3.36	1.54±3.31	64.6±3.45	−2.58±1.87
	Calm	Placebo	62.5±3.01	−5.50±2.28	63.3±4.09	−5.65±3.67
		75 mg	65.9±3.02	−6.73±2.37	64.9±3.91	−11.4±3.94
		150 mg	62.3±2.58	−5.38±3.55	60.6±3.90	−10.3±3.95
Caffeine research VAS	Relaxed	Placebo	59.9±3.33	−3.50±3.73	61.3±3.99	−2.72±4.09
		75 mg	62.3±3.67	−3.92±3.47	62.8±4.97	−9.00±3.19
		150 mg	56.7±3.88	−6.33±6.01	55.0±4.40	−2.59±4.50
	Alert	Placebo	55.3±3.77	0.83±4.13	54.9±4.40	−3.05±5.63
		75 mg	52.1±4.54	9.42±4.63	53.0±4.89	5.27±5.89
		150 mg	48.5±4.66	8.38±5.26	58.0±4.26	3.27±4.39
	Jittery$^{T\times G}$	Placebo	34.5±3.95	−3.00±3.46	34.7±4.74	14.6±5.53
		75 mg	29.1±3.79	4.46±4.00	36.2±4.95	8.82±4.52
		150 mg	30.6±3.78	14.2±4.80***	40.6±5.08	4.23±4.96
	Tired^{T}	Placebo	53.0±4.81	1.83±4.30	49.9±5.79	2.77±5.29
		75 mg	59.3±4.75	−12.8±4.68*	52.8±5.33	−3.82±6.34
		150 mg	58.2±4.92	−14.6±6.06*	51.9±4.68	−7.18±3.20
	Tense	Placebo	39.2±3.53	1.88±3.87	33.8±4.74	3.09±3.36
		75 mg	36.5±4.69	6.13±4.37	35.4±4.95	4.41±3.84
		150 mg	35.5±4.89	4.96±6.71	33.2±5.52	5.46±4.07
	Headache	Placebo	23.8±4.92	3.96±2.51	26.4±5.05	9.68±3.32
		75 mg	24.9±5.34	2.25±3.13	26.9±5.18	3.41±3.66
		150 mg	27.4±5.54	−0.33±4.44	26.1±5.20	8.59±4.02
	Overall mood	Placebo	63.0±3.29	0.29±2.24	66.4±2.97	−3.18±3.08
		75 mg	61.9±3.32	0.79±3.50	65.8±3.93	−0.73±3.37
		150 mg	56.5±4.06	7.75±3.91	66.4±3.10	−2.27±3.67
	Mental fatigue^{T}	Placebo	46.3±4.22	1.63±3.96	46.6±4.72	6.77±5.00
		75 mg	45.2±5.04	−4.71±5.02	46.9±4.80	−9.59±5.37*
		150 mg	52.2±4.65	−12.6±5.12*	42.9±5.01	1.50±3.45
Caffeine research VAS factors	**Alertness**^{T}	Placebo	51.2±3.72	−0.50±3.34	52.5±4.40	−2.91±4.94
		75 mg	46.4±4.24	11.1±4.26*	50.1±4.69	4.55±5.56
		150 mg	45.2±4.61	11.5±5.16*	53.1±4.07	5.23±3.45
	Tension	Placebo	39.7±3.01	2.69±2.77	36.3±4.07	2.91±3.07
		75 mg	37.1±3.67	5.02±3.04	36.3±4.68	6.71±3.55
		150 mg	39.4±4.08	5.65±5.89	39.1±4.17	4.02±3.19

Baseline and change from baseline scores are presented for consumers and non-consumers. Scores presented in bold depict significant main effects from the primary analysis ANOVA ($p<0.05$).

T treatment effects, *T*×*G* treatment by group interactions

Significant effects from the secondary analysis' planned comparisons are represented by asterisk(s) indicating which group(s) were affected and by which treatment(s) (*$p<0.05$, ***$p<0.005$).

[$F(2,46)=4.86$, $p=0.012$]. Planned comparisons revealed a significant improvement following 150 mg [$t(46)=2.85$, $p=0.007$].

Mood measures were also affected with consumers becoming more jittery [$F(2,46)=4.79$, $p=0.013$]. Planned comparisons showed this effect was apparent in response to the 150 mg dose [$t(46)=3.09$, $p=0.003$]. There was a significant alteration in alertness in response to treatment [$F(2,46)=3.87$, $p=0.028$]. Planned comparisons revealed there were significant increases following doses of 75 mg [$t(46)=2.37$, $p=0.022$] and 150 mg [$t(46)=2.45$, $p=0.018$]. Again, this effect was primarily due to a reduction in tiredness [$F(2,46)=4.93$, $p=0.013$]. Planned comparisons revealed that this was significant following doses of 75 mg [$t(46)=2.55$, $p=0.014$] and 150 mg [$t(46)=2.86$, $p=0.006$]. There was also a significant main effect of treatment on

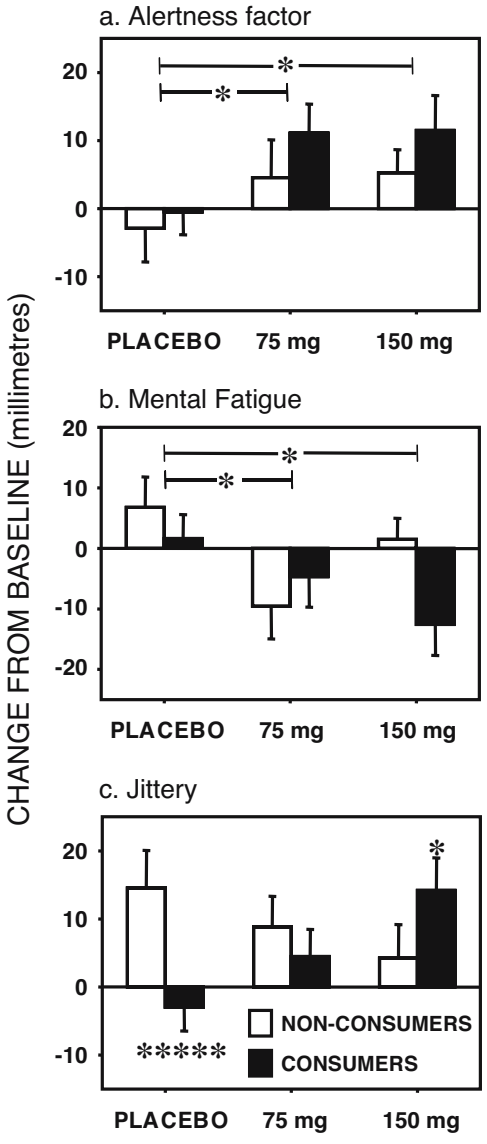

Fig. 2 Means (±SEM) change from baseline mood scores for consumers and non-consumers following placebo, and 75 and 150 mg caffeine. Significant treatment effects, compared with placebo (**a**, **b**), and consumer–non-consumer differences (**c**) are shown (*p<0.05; *****p<0.0005)

mental fatigue [F(2,46)=3.48, p=0.039]. Planned comparisons revealed there was a significant decrease following 150 mg [t(44)=2.63, p=0.011].

Non-consumers

There was a significant main effect of treatment on digit vigilance accuracy [F(2,46)=4.31, p=0.019]. Planned comparisons revealed a significant improvement following the 150 mg dose [t(46)=2.71, p=0.009]. Digit vigilance reaction time was also significantly affected by treatment [F(2,46)=4.00, p=0.025]. Planned comparisons showed there were significant improvements following doses of 75 mg [t(46)=2.66, p=0.011] and 150 mg [t(46)=2.16, p=0.036]. There was a significant improvement in numeric working memory reaction time [F(2,46)=4.20, p=0.021]. Planned comparisons revealed this effect was apparent following 150 mg [t(46)=2.90, p=0.006]. There was also a significant improvement in sentence verification accuracy [F(46)=3.78, p=0.030]. Planned comparisons showed these improvements were evident following doses of 75 mg [t(46)=2.56, p=0.014] and 150 mg [t(46)=2.14, p=0.038]. There was a significant main effect of treatment on delayed picture recognition reaction time [F(2,46)=3.58, p=0.036]. Planned comparisons revealed there was a significant detriment following a dose of 150 mg [t(46)=2.37, p=0.022].

Mood measures were also affected. There was a significant main effect of treatment on subjective ratings of mental fatigue [F(2,42)=3.28, p=0.047]. Planned comparisons revealed that there was a significant reduction in mental fatigue following 75 mg [t(42)=2.51, p=0.016].

Discussion

In line with many previous studies these results show that caffeine improves cognitive performance and mood in healthy, young adults in a manner which cannot be explained by withdrawal alleviation. Firstly, there were no baseline differences between the consumer groups and, secondly, positive effects of caffeine were found in both consumers and non-consumers. Irrespective of caffeine habit, caffeine led to a reduction in reaction time on a number of tasks relating to attention and working memory as well as improving sentence verification accuracy. Mood measures relating to arousal were also significantly improved in both groups. The alleviation of withdrawal model states that caffeine should only lead to improvements in caffeine consumers who are in a state of withdrawal and should not elicit positive effects in non-consumers who are not withdrawn. These findings provide strong support for absolute enhancement of mood and performance following acute caffeine administration.

An analysis of mean baseline scores from the current experiment also fails to support a withdrawal alleviation model. Only two significant differences in the performance of consumers versus non-consumers were noted, with consumers performing better than non-consumers on the serial sevens and serial threes subtraction tasks. The withdrawal alleviation model posits that consumers' performance will be impaired as a result of caffeine withdrawal, this was clearly not the case here. The results are consistent with Rogers et al.'s (2003) findings of no significant differences between non-consumers' and acutely withdrawn consumers' performance of a simple reaction time task at baseline. Smit and Rogers (2000) also compared baseline performance in caffeine-deprived low and higher caffeine consumers and found that higher consumers performed significantly better on an RVIP task than low consumers. In line with this lack of cognitive effect due to consumption grouping, the present study also

failed to support previous reports suggesting that consumers' subjective mood state is significantly impaired during caffeine withdrawal (Goldstein et al. 1969; Rogers et al. 2003; Richardson et al. 1995). However, it should be noted that in the second of two reported experiments, Rogers et al. (2003) also failed to replicate the finding of reduced baseline alertness in consumers. This suggests that these effects are fragile and may be influenced by non-pharmacological processes such as expectancy (since presumably consumers are aware that they are caffeine deprived). Such effects will be less marked when examining placebo change from baseline scores rather than baseline scores when assessing withdrawal effects (again, we found no evidence for caffeine withdrawal using such an analysis). Studies comparing the effects of caffeine delivered in both novel vehicles and in coffee beverages may help to disentangle these pharmacological, expectancy and conditioning effects.

Turning to the primary analysis examining treatment × group effects, the results here support previous demonstrations of absolute improvements following caffeine. In two experiments, Rogers et al. (2003) found that caffeine was capable of improving alertness in consumers and non-consumers alike. Warburton et al. (2001) found that a caffeinated taurine drink produced improvements in verbal reasoning in those who had been allowed ad libitum caffeine consumption. Smit and Rogers (2000) also demonstrated that caffeine doses as low as 12.5 mg were equally capable of producing improvements in simple reaction time in low and higher caffeine consumers.

Whilst not wishing to over-interpret the pattern of enhancement found here, the data do support previous reports suggesting that caffeine preferentially improves performance on tasks assessing attention and vigilance (as reflected by improvements on both simple reaction time and digit vigilance reaction time for both doses and for both consumer groups; see Fig. 1). It has been suggested that such effects may be the result of adenosine blockade by caffeine causing acute upregulation of activity within the ascending cholinergic activating system (Warburton et al. 2001). It has previously been argued that cholinergic modulation is unlikely to be the exclusive target for the effects of caffeine (Scholey and Kennedy 2004). Indeed, one might expect to see more widespread effects on attentional measures if this were the case. The only other cognitive measure which was robustly affected across groups by both doses was sentence verification (Fig. 1). The neurochemical substrates underpinning this task are not known; however, the task draws on aspects of cognitive flexibility and retrieval of semantic information. The former is also required for logical reasoning, which was unaffected in this study (Table 1). It is also worth noting that sentence verification has been shown to be robustly sensitive to caffeine in a series of studies by Smith's group (Nguyen-Van-Tam 2002). While this pattern of results is interesting, it has been argued that caffeine preferentially targets tasks of vigilance performed over a long period. With the possible exception of the 5-min RVIP, the tests used here were of a relatively short period. Even the 'digit vigilance' task was of relatively short duration (1 min) and as such it could be argued that it is not a 'true' test of vigilance. It would be interesting to examine the effects on such tasks using the methodology employed here.

There were no consistent effects on working memory measures (Fig. 1). Numeric working memory reaction time was improved by the 150 mg dose alone, while there were group differences only on spatial working memory sensitivity (with consumers performing better than non-consumers independent of treatment). Interestingly, the latter effect was similar to the results for false alarms during the RVIP (a task with a large working memory component). Further work is necessary in order to draw firm conclusions about caffeine effects on working memory.

Turning to the mood measures, the data here confirm that caffeine can improve self-rated alertness. Interestingly, the effect was found only for the caffeine research VAS and not the Bond–Lader scales. In the latter measure the 'alertness' factor is derived from nine subscales, while in the former it is an aggregate of two measures 'alert' and 'tired'. It is clear that the effects on this scale are largely due to a reduction in rating on the 'tired' subscale (Table 3). This is supported when examining the effects on the single 'mental fatigue' scale which was sensitive to both doses of caffeine and across both groups and which showed a pattern of results which was largely a mirror image of the affected 'alertness' scale (Fig. 2). The separate analyses of consumers and non-consumers suggested that consumers' alertness was more sensitive to the effects of caffeine. This broadly supports the results of Goldstein et al. (1969), who found only consumers were affected on a mood cluster which included measures of 'alert', 'attentive', 'observant', 'able to concentrate'. On the other hand, our results show that both consumers and non-consumers self-ratings of mental fatigue were affected (albeit at different doses).

The only interaction between group and treatment effects was found in participants' ratings of jitteriness. Many studies report that caffeine increases jitteriness (Rogers et al. 2003; Richardson et al. 1995), particularly in non-consumers. However, in this case non-consumers rated themselves as more jittery than consumers following placebo and less jittery than consumers following 150 mg caffeine.

The results of the primary analysis do not support withdrawal alleviation models. However, the secondary analyses examining each group's scores separately did reveal some differences (and similarities) between the caffeine responses of habitual consumers and habitual non-consumers of caffeine. Both groups' sentence verification accuracy and mental fatigue were improved by caffeine. Of the five measures which were affected in consumers, three were mood items ('jittery', 'alert' and 'mental fatigue'), and two were performance outcomes (accuracy of both sentence verification and RVIP). For non-consumers, one measure, delayed picture recognition reaction time, was impaired. Of the five measures which were enhanced by a caffeine challenge, only one ('mental

fatigue') was a mood item, while the remaining four were performance outcomes (accuracy of sentence verification and digit vigilance and speed of digit vigilance and numeric working memory).

In its strictest form the withdrawal alleviation model would predict detrimental performance in overnight withdrawn caffeine consumers and no beneficial effects of caffeine in non-consumers. Clearly, this interpretation is overly simplistic and these results indicate a more complex picture. The effects of caffeine were positive in both groups and there was no evidence for withdrawal as indicated by the groups' equivalent performance and mood at baseline following overnight caffeine abstinence. Additionally, non-consumers' performance and fatigue levels were improved following a caffeine challenge. On the other hand, absolute enhancement by caffeine is not supported unreservedly since the secondary analysis revealed that consumers and non-consumers exhibited slightly different (but not mutually exclusive) responses to caffeine as outlined above. It may be that caffeine use is more strongly reinforced through mood benefits and it is these effects which determine whether an individual will become a habitual caffeine consumer or a habitual non-consumer.

Whilst there are problems with relying on self-report caffeine consumption questionnaires in order to determine whether someone is a caffeine consumer or non-consumer, this method is one which is widely used in this area of study and it seems unlikely that people would be deceptive in this matter. However, it may be possible that they were unaware of caffeine consumption in certain products. Possibly future studies of this nature should take salivary samples at recruitment to determine 'typical' caffeine levels. Certainly, compliance to caffeine abstinence was confirmed by analysis of salivary caffeine levels. A further issue is the question of whether the non-consumer group used here can be said to be free of the effects of caffeine withdrawal. It might be that even rather low or intermittent dietary intakes of caffeine cause sufficient adenosine receptor upregulation for significant negative effects to be precipitated on caffeine withdrawal. This issue could only be fully addressed by comparing habitual consumers with both habitual non-consumers and those who abstain from caffeine completely. However, the fact that the two groups were affected differently on certain measures does provide some support for the case for them being different populations.

In conclusion, the current study shows that doses of caffeine in the range of those found in a typical cup of coffee (Gray 1998) can improve mood and cognitive performance in caffeine consumers and non-consumers alike. It is not possible to state that either of the doses administered here (75 and 150 mg) had a greater impact on performance and mood. Rather it is apparent that response to the different doses varies with regard to task. The main purpose of this study was to examine the effects of realistic everyday doses of caffeine in consumers and non-consumers using sensitive measures of mood and cognitive performance. These findings overwhelmingly support absolute benefits over alleviation of withdrawal.

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