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Faster but not smarter: effects of caffeine and caffeine withdrawal on alertness and performance

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Short title: Alerting and performance effects of caffeine use

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Abstract

Rationale Despite 100 years of psychopharmacological research the extent to which caffeine consumption benefits human functioning remains unclear. *Objectives* To measure the effects of overnight caffeine abstinence and caffeine administration as a function of level of habitual caffeine consumption. *Methods* Medium-high (n = 212) and non-low caffeine consumers (n = 157) completed self-report measures and computer-based tasks before (starting at 10.30 AM) and after double-blind treatment with either caffeine (100 mg then 150 mg) or placebo. The first treatment was given at 11.15 AM and the second at 12.45 PM, with post-treatment measures repeated twice between 1.45 PM and 3.30 PM. *Results* Caffeine withdrawal was associated with some detrimental effects at 10.30 AM, and more severe effects, including greater sleepiness, lower mental alertness, and poorer performance on simple reaction time, choice reaction time and recognition memory tasks, later in the afternoon. Caffeine improved these measures in medium-high-high consumers, but, apart from decreasing sleepiness, had little effect on them in non-low consumers. The failure of caffeine to increase mental alertness and improve mental performance in non-low consumers was related to a substantial caffeine-induced increase in anxiety/jitteriness that offset the benefit of decreased sleepiness. Caffeine enhanced physical performance (faster tapping speed and faster simple and choice reaction times) in both medium-high and non-low consumers. *Conclusions* While caffeine benefits motor performance and tolerance develops to its tendency to increase anxiety/jitteriness, tolerance to its effects on sleepiness means that frequent consumption fails to enhance mental alertness and mental performance.

Key words: Caffeine, Tolerance, Withdrawal, Mental performance, Physical performance, Reaction time, Cognition, Alertness, Sleep, Anxiety

Introduction

Judged by the amount and frequency of consumption, caffeine is humankind's favourite drug. Caffeine is consumed worldwide predominantly via tea and coffee, its popularity deriving, at least in part, from the perception that it is a helpful, but mostly harmless, psychostimulant. In fact, through antagonism of the action of endogenous adenosine at adenosine A_1 and A_{2A} receptors, caffeine has various physiological and behavioural effects (Fredholm et al. 1999). For example, as well as increasing wakefulness, caffeine raises blood pressure, causes tremor (reduces hand steadiness), enhances physical performance, and is mildly anxiogenic (Heatherley et al. 2005; James 2004; Rogers et al. 2010; Warren et al. 2010). However, determining the benefits or otherwise of caffeine consumption is complicated by the potential for tolerance to develop to its effects with repeated frequent exposure. It is instructive therefore to compare the effects of caffeine in individuals who consume caffeine-containing products frequently with those who do not (or who have abstained from caffeine for a lengthy period of time – long term withdrawn consumers) (James and Rogers 2005). Rather few studies have done this.

The first systematic and rigorous human psychopharmacological study of caffeine was published 100 years ago (Hollingworth 1912). The research was commissioned by the Coca-Cola Company in defence of a lawsuit accusing it of adding a harmful ingredient, namely caffeine, to Coca-Cola (Benjamin 2010). Hollingworth's approach was an intensive study of a small numbers of individuals, 15 in total, over 45 days. These participants received caffeine, in doses ranging between 65 and 390 mg, and placebo administered in capsules and 'syrup' before and after completing repeated tests assessing 'mental and motor' performance. (Note that currently, regular Coca-Cola currently contains 30 mg of caffeine per 330 ml serving and, as drunk in the UK, on average tea contains 40 mg, instant coffee 55 mg and

ground coffee 105 mg of caffeine per typical serving (Heatherley et al. 2006)). Hollingworth's results showed that caffeine increased tapping speed (participants were required to tap a metal rod as quickly as possible on a metal surface) and decreased hand steadiness (measured by the number of contacts made between a 2.5 mm diameter metal rod, held in the dominant hand with the arm outstretched, and the side of a 6 mm hole in a brass plate). At doses of 65 and 130 mg caffeine improved performance on a test of coordination (requiring insertion of a rod into holes on a board), but at the highest dose (390 mg) coordination performance was impaired, probably due to the marked increase in tremor at that dose. Other results, for choice reaction time, number cancellation, calculation and word retrieval tasks were less clear, but suggested some enhancement of performance. Hollingworth (1912) commented that "the widespread consumption of caffeinic beverages... seems to be justified by the results of this experiment" (pages 165-166). However, 50 years later Weiss and Laties (1962) on reviewing Hollingworth's study and subsequent research on caffeine and amphetamines concluded that "the amphetamines seem not only more effective (in enhancing performance) than caffeine, but less costly in terms of side effects" (page 32). They were concerned by the evidence that caffeine caused nervousness, irritability and headache and that it disturbed sleep, though they also concluded that "caffeine does not cause physical dependence" (page 32).

Today, making a distinction between dependence and addiction, we would argue that, while caffeine has a low potential for abuse, frequent caffeine consumers are caffeine dependent, in that withdrawal of caffeine has adverse effects, including lowered alertness, slowed mental performance and headache (Rogers and Smith 2011). Hollingworth's research, while exemplary in many respects, may have confounded effects of caffeine with effects of caffeine withdrawal. In his main set of experiments participants received caffeine and placebo on alternate days for 27 days in total, with the doses of caffeine increasing from 65 to

390 mg (two days at each dose). It is likely that at higher doses the effects of caffeine will have been assessed against a background of more marked caffeine dependence and acute withdrawal.

The different effects of caffeine as a consequence of recent exposure to caffeine are evident from another landmark study. Goldstein et al. (1969) measured alertness, mood and associated states after caffeine (150 and 300 mg) and placebo in 'housewives' who were reported to be either non-consumers of coffee (n=18) or who drank at least 5 cups of coffee per day (n=38). (Note that it is implied, though not stated explicitly, by Goldstein et al. that the non-consumers of coffee, consumed little or no caffeine from other sources, so these participants can be regarded as non-consumers, or at least very low consumers of caffeine.) Participants consumed the treatments blind (each on three separate days) after breakfast as decaffeinated coffee, or decaffeinated coffee with caffeine added, having abstained from all caffeine-containing drinks after supper the previous day. There were several striking results for alertness. The first was that the caffeine consumers rated themselves as feeling less alert before administration of the treatments (caffeine or placebo) than did the non-consumers. Second, over the next 2 hours caffeine versus placebo increased alertness in consumers; however, even after the highest dose caffeine, their alertness increased only to the level of alertness rated by non-consumers when they received placebo. Third, caffeine barely affected alertness in non-consumers, despite there being considerable room for an increase in scores (maximum alertness score for the placebo treatment was 1.8 on a 0-3 point scale).

We have cited these findings as part of the evidence that frequent caffeine consumption provides no net benefit for alertness and, as a consequence, for performance of mental tasks requiring sustained attention (James and Rogers 2005). This would indicate (complete) tolerance to the alerting effects of caffeine in frequent consumers (e.g., Zwyghuizen-Doorenbos et al. 1990) – with repeated frequent exposure to caffeine, changes to

adenosine signalling develop to oppose its effects, causing alertness to decline on withdrawal of caffeine (Fredholm 1999). However, there is a problem with this explanation, as it predicts increased alertness on initial exposure to caffeine, whereas Goldstein et al. (1969) found no effect of caffeine on alertness in non-consumers. On the other hand, some authors, including ourselves, have reported finding that caffeine can increase alertness in non- or low caffeine consumers (Rogers et al. 2003; Smith et al. 2006), and, more generally, the withdrawal reversal explanation of effects of caffeine in higher consumers has been widely disputed (e.g., Smith et al. 2006; Childs and de Wit 2006; Dews et al. 2002; Haskell et al. 2005).

In light of these disagreements, the aim of the present study was to characterise further the responses to caffeine of non-low and medium-high caffeine consumers. In particular, we set out to investigate the relationship between the alerting and mental performance effects of caffeine. For this purpose we assessed specifically mental alertness, using the cluster of descriptors 'I feel mentally alert / attentive / able to concentrate / observant.' These descriptors are the same as those used by Goldstein et al. (1969), except we included the descriptor 'mentally alert' rather than 'alert'. Arguably, with or without the word 'mentally' this cluster measures mental alertness, rather than a perhaps a more general state of wakefulness, and from here on in we will use the term mental alertness when referring to both the present study and Goldstein's et al. (1969) study. Of course, it is to be expected that mental alertness would co-vary with sleepiness/wakefulness; however, here, unlike in our earlier report of some of these data (Rogers et al. 2010), we treated sleepiness/wakefulness and mental alertness as separate dependent variables. Additionally, based on extensive evidence of mild anxiogenic effects of caffeine (Rogers et al. 2010), we included measures of anxiety/jitteriness. Notably, Goldstein et al. (1969) found that caffeine increased jitteriness (their label for the cluster comprising the descriptors jittery, nervous and shaky) in non-consumers but not in medium-high consumers. We also measured the motor effects of

caffeine using a tapping task, because our tests of mental performance, similar to those employed in many relevant previous studies, required a motor response (i.e., key presses).

Based on withdrawal reversal (James and Rogers, 2005), the main hypotheses for the present study were that: (1) mental alertness of medium-high caffeine consumers would be lowered after acute caffeine withdrawal (2), administration of caffeine would subsequently restore mental alertness to 'normal' for the time of day (using non-low consumers' placebo level as a benchmark), and (3) these effects of caffeine and caffeine withdrawal on mental alertness would be mirrored by and related to their effects on sleepiness and performance of tasks requiring sustained attention. Additionally, based on results from Hollingworth (1912) and from subsequent studies (e.g., Warren 2010), we predicted that caffeine would enhance motor performance. We also examined the interrelationships between the effects of caffeine, sleepiness, anxiety, mental alertness and performance.

Method

Participants

The results reported here are from a total of 369 participants for whom there was evidence (salivary caffeine concentration) confirming their caffeine consumer status and compliance with the requirement to abstain from caffeine overnight before testing (see Rogers et al. 2010, for details), and complete data available for mental alertness, sleepiness, anxiety/jitteriness and task performance. These participants were aged between 18 and 62 years, and were non- or light smokers (≤5 cigarettes or equivalent a day – smoking was not permitted during the test day until after participants left the laboratory). The study protocol was reviewed and approved by the University of Bristol's, Department of Experimental Psychology Human Research Ethics Committee. Participants gave their informed, signed consent prior to participating in the study.

Design and treatments

Based on information recorded in a caffeine intake questionnaire (Rogers et al. 2010) the participants were divided into 'non-low' and 'medium-high' caffeine consumers (caffeine intake of <40 mg/d and ≥40 mg/d, respectively) and randomly assigned to receive caffeine (caffeine BP anhydrous powder) at 11.15 AM (100 mg) and 12.45 PM (150 mg) or placebo (cornflour) on both occasions. Each of these treatments was administered double blind in a single, white, size 1 cellulose capsule. They were identical in appearance, and were swallowed with 50 ml of room temperature water. The two doses of caffeine ensured that systemic caffeine concentration during the afternoon modeled that expected for individuals consuming two to three cups of ground coffee previously that day.

(Note that the caffeine questionnaire measured the frequency of participants' consumption of caffeine-containing products during the week preceding testing. Caffeine intake was calculated from consumption frequency using information from various sources on the caffeine content of these products (teas, coffees, colas, etc.). The 40 mg/d criterion is supported by the results of our previous analyses comparing effects across four levels of caffeine consumption in this cohort of participants (Rogers et al. 2010, Figure 1)).

Measures

The test battery, which included the mental performance and motor tasks and mental alertness etc. rating scales, was programmed using E-Prime 1.0 (Psychology Software Tools, Science Plus Group bv, 9747 AA Groningen, The Netherlands) and run on networked PCs with 15-in colour monitors and standard QWERTY keyboards. These tasks and rating scales were presented in the following order: tapping, mental alertness etc, recognition memory, simple

reaction time and choice reaction time, and the full battery took approximately 30 minutes to complete.

For the tapping task, using their dominant hand, participants were required to tap the spacebar on the computer keyboard as many times as possible within 30 seconds.

Mental alertness, sleepiness and anxiety/jitteriness were measured using the following items from the Mood, Alertness and Physical Sensations Scales (MAPSS) (Rogers et al. 2010): I feel mentally alert / attentive / able to concentrate / observant; I feel sleepy / drowsy / half awake; I feel anxious / tense / nervous /on edge combined with I feel jittery / shaky. These are similar to three of Goldstein's et al. (1969) eleven items (clusters) (i.e., A = alert, attentive, observant, able to concentrate; E = sleepy, tired, drowsy, half-awake; C = jittery, nervous, shaky). Our participants indicated their current state using the horizontal number pad on the computer keyboard, where 1 represented 'not at all' and 9 represented 'extremely' (adjusted to a 0 to 8 scale for the presentation of the results here).

The recognition memory task was similar to the 'digit vigilance' task used by Haskell et al. (2005). Five to-be-remembered digits (0-9) were presented sequentially for 500 ms at 100 ms intervals. These were followed by 30 probe digits also presented sequentially. For each of these 30 digits participants were required to indicate whether or not it had occurred in the preceding series of five digits. They did this by pressing keys labeled Y or N on the computer keyboard (Y = J key and N = F key on the keyboard). This was repeated a total of six times with different probe and to-be-remembered digits. The dependent variable was the total number of errors made (i.e., false positives plus false negatives).

For the (variable fore-period) simple reaction time task participants were instructed to press the space bar as quickly as possible upon the detection of a stimulus, a small star, in the centre of the computer screen. There was a variable stimulus onset of 1, 2, 3, 4, 7, 9, 12 and 15 s randomised within cycles of eight trials (presentations). The task comprised eight cycles

(64 trials) in total, which for analysis were divided into four blocks each comprising two successive cycles. The dependent variable was mean reaction time per block.

For the (two-) choice reaction time task each trial began with the presentation of three warning crosses in the centre of the computer screen, which were replaced after 500 ms by a target letter A or B. This target was presented alone or accompanied by distracter stimuli on either side. The distracters were stars, or letters (A or B) the same as or different from the target letter, that were positioned either near or far from the target. Participants were required to indicate as quickly and accurately as possible whether the target was A or B by pressing keys labelled A and B on the computer keyboard (A = J key and B = F key). A total of 384 trials were completed. Data from this task can be used to derive a measure of focus of attention as we did in a previous study of the effects of caffeine and caffeine withdrawal (Rogers et al., 2005). For the present report, the dependent variables of interest were mean reaction time and number of errors.

Procedure

Between two and six participants were tested on any single day. They arrived at the laboratory at 9.30 AM having been instructed to abstain from caffeine consumption from at least 7 PM the previous evening, and they left at 4.15 PM. An initial briefing session was held in a communal room, and this same room was used for rest periods, lunch (a light lunch was served at 12.50 AM) and debriefing. The participants completed the mental performance and tapping tasks and the mental alertness, etc. ratings in a room close by, where each individual was accommodated in separate, private booth. They completed this battery of tasks a total of four times: before treatment (baseline, starting at 10.30 AM), starting 45 minutes after the first dose of caffeine or placebo, and starting 60 and 135 minutes after the second

dose of caffeine or placebo. This was part of a larger protocol described in fuller detail elsewhere (Rogers et al., 2010).

Data analysis

Data were analysed using analysis of variance (ANOVA). Data from measures taken before administration of caffeine or placebo (pre-treatment baseline) were analysed for effects of consumer status (non-low versus medium-high consumers). Post-treatment data were analysed for the effects of caffeine (caffeine versus placebo) and consumer status. In order to simplify the presentation, only the results from measures taken after the administration of the second dose of caffeine (means of the data from second and third task battery) are reported in detail here. Block (four levels) was additionally included as a repeated measures factor (Greenhouse-Geisser correction applied) in the analysis of the data from the simple reaction time task. For the post-treatment data multiple paired comparisons were made using Tukey's Honestly Significant Difference test (Ferguson & Takane, 1989). In further analyses of the effects of caffeine, pre-treatment baseline scores were included as a covariate. Because their scores for a majority of variables differed or tended to differ at baseline, these particular analyses were carried out separately for non-low and medium-high consumers (the purpose was to control for baseline differences within consumer status groups not between these groups). Gender was included as a fixed factor, and age and smoking status (smoking tended to be associated with caffeine intake – see below) were included as covariates in all of the above analyses. Standard multiple linear regression (Tabachnick and Fidell, 2007) was used to examine the contributions of the effects of caffeine on mental alertness and tapping speed to its effect on simple reaction time. (Out of the four tasks, the simple reaction time task had most equally both motor and vigilance components.) We also examined the contributions of caffeine's effects on sleepiness and anxiety/jitteriness to its

effect on mental alertness. These analyses were done for only those participants who received caffeine and separately for non-low and medium-high caffeine consumers. Alpha was set at 0.05 (2-tail).

Results

There were 157 non-low and 212 medium-high caffeine consumers (mean ± SD caffeine consumption = 10.2 ± 11.6 and 235 ± 146 mg/d, and mean ± SD age = 31.7 ± 12.1 and 33.8 ± 12.7 years, respectively), of whom 85 and 109 were female, and 21 and 41 were smokers. Mean ± SD pre-treatment (baseline, sample taken at 11.10 AM) salivary caffeine concentration for non-low caffeine consumers were 0.019 ± 0.036 µg/ml (maximum value = 0.17 µg/ml; participants in this group with values >0.2 µg/ml were excluded, Rogers et al. 2010), and for medium-high consumers these values were 0.29 ± 0.38 µg/ml (max. = 1.97 µg/ml; participants in this group with values >2.0 µg/ml were excluded, Rogers et al. 2010). Corresponding values for salivary concentration of the caffeine metabolite paraxanthine were 0.021 ± 0.036 µg/ml (maximum = 0.18 µg/ml) and 0.29 ± 0.30 µg/ml (maximum = 2.62 µg/ml).

At 10.30 AM after overnight caffeine abstinence (pre-treatment baseline) the medium-high caffeine consumers performed worse on the choice reaction time (errors) and simple reaction time tasks than did the non-low consumers, and they were also somewhat less mentally alert and more sleepy (Table 1).

The results for the effects of caffeine and consumer status on mental alertness, sleepiness, anxiety/jitteriness, mental performance and tapping performance are summarised in Table 1 and Fig. 1. There was a significant main effect of caffeine for all measures except recognition memory (p = .065), a significant consumer status effect for all but anxiety/jitteriness, choice reaction time and tapping performance, and a significant or

marginally insignificant caffeine by consumer status effect for all but sleepiness and tapping performance. Generally, the difference between caffeine and placebo treatments was larger for medium-high consumers, with the striking result being lower mental alertness, greater sleepiness and, with the exception of the tapping task, poorer performance on all tasks in medium-high consumers who received placebo than in the other three groups (Fig. 1). Except for anxiety/jitteriness, caffeine affected medium-high consumers' responses on all measures: sleepiness, mental alertness, simple reaction time, choice reaction time, choice reaction time errors, recognition memory, and tapping speed († in Fig. 1). Caffeine did not affect mental alertness, or the number of errors made on the recognition memory and choice reaction time tasks in non-low consumers, though it did reduce their sleepiness, increase their anxiety/jitteriness and speed their tapping performance, and to a smaller extent it also speeded their choice reaction time and simple reaction time performance († in Fig. 1).

Block was included in the analysis of simple reaction time performance. The caffeine by consumer status by block interaction was significant, $F(2.44, 874.8) = 3.51$, $p = 0.02$. Fig. 2 shows that, as well being much slower overall on this task, medium-high consumers who received placebo displayed a marked deterioration in performance across block. The medium-high consumers who received caffeine and the non-low consumers displayed no such deterioration.

Results of the multiple linear regression analyses are shown in Table 2. For medium-high caffeine consumers the effects of caffeine on mental alertness and on tapping speed independently predicted its effect on simple reaction time performance. In turn, caffeine's effect on mental alertness was predicted by its effect on sleepiness. For non-low consumers, in contrast, only the effect of caffeine on tapping speed predicted its effect on simple reaction time performance, and caffeine's effects on both sleepiness and anxiety/jitteriness contributed to its effect on mental alertness. Note that the latter (anxiety/jitteriness and mental alertness)

were *inversely* related. Further analyses showed that for both non-low and medium-high consumers the effects of caffeine on sleepiness and anxiety/ jitteriness were unrelated (non-low consumers, r = .07, $p > .1$; medium-high consumers, r = .04, $p > .1$), as were the effects of caffeine on mental alertness and tapping performance (non-low consumers, r = –.06, $p > .1$; medium-high consumers, r = –.15, $p > .1$). Lastly, before caffeine administration (baseline), mental alertness and tapping speed predicted simple reaction time performance; and sleepiness, but not anxiety/jitteriness, predicted mental alertness. Here, the pattern of results did not differ for non-low and medium-high caffeine consumers (data not shown).

Discussion

The present study helps to resolve some important questions that remain after a century of research on the effects of caffeine on human behaviour. In particular, in line with the study hypotheses, they strongly support the claim that medium-high caffeine consumers gain *no* acute net benefit for mental alertness and mental performance from their habit (James and Rogers 2005). That is, the increase in mental alertness experienced by medium-high caffeine consumers after taking caffeine, and the associated improvement in mental performance, represent a return to the normal state of affairs (i.e., reversal of adverse effects of caffeine withdrawal), rather than enhancement to above the normal state. The present results also shed light on the, perhaps surprising, failure of caffeine to reliably increase mental alertness in individuals consuming little or no caffeine in their diet (first reported by Goldstein et al. in 1969) – although caffeine reduced sleepiness in non-low consumers this appears to have been offset by an increase in anxiety/jitteriness, resulting in no net benefit for mental alertness (see below). In contrast to mental alertness, the results for the tapping task demonstrate that administration of caffeine increases motor speed irrespective of frequency of habitual caffeine consumption. As discussed below, these different effects of caffeine on mental

alertness and motor speed would, in turn, appear to explain rather well the observed pattern of effects for simple reaction time, choice reaction time and memory performance.

Effects of acute caffeine abstinence

At 10.30 AM after overnight caffeine abstinence medium-high caffeine consumers performed more poorly on the simple reaction time and choice reaction time (error measure) tasks than did the non-low consumers. Correspondingly, their mental alertness was somewhat lower and their sleepiness somewhat higher than for the non-low consumers. Similar results for mental alertness and sleepiness have been reported previously (Goldstein 1969; Rogers et al. 2003). These caffeine consumer status differences at 'baseline' were, however, small in magnitude, and other studies have not found such differences in alertness (Haskell et al. 2005; Smith et al. 2006) or performance (Rogers et al. 2003; Haskell et al. 2005; Smith et al. 2006). Probably, this is due, at least in part, to lack of statistical power. Individual differences, particularly in performance, are likely to be large in comparison with the effects of a fairly short period of caffeine withdrawal (similar to or at most 2-3 hours longer than the period of overnight caffeine abstinence typical for medium-high caffeine consumers). The present study had a relatively large sample size, and controlling for gender and age in the analyses reduced the amount of variance in performance unaccounted for. It is also the case that misclassification of 'medium-high consumers' as 'non-low consumers' (and vice versa), and failure of medium-high consumers to abstain from caffeine overnight as instructed, will cause group differences in performance and alertness to be underestimated (see introduction). Measurement of pre-treatment salivary caffeine concentration helped avoid these problems here. Nonetheless, 42% of our non-low consumer group had detectable levels of caffeine and/or paraxanthine in their saliva. (Paraxanthine is the major metabolite of caffeine in humans and is also psychoactive (Okuro et al. 2010).) Perhaps at least some of these

individuals were in fact consuming sufficient caffeine in their diet to cause them to experience significant adverse effects when caffeine was withdrawn. This, however, is even more likely to apply to studies by Haskell et al. (2005) and Smith et al. (2006) which found no consumer group differences in morning alertness and mental performance. In these studies baseline salivary caffeine concentrations for 'non-consumers' were 0.36 µg/ml (mean value) (Haskell et al. 2005) and ≤ 2 µg/ml (maximum cut off value, no mean value given) (Smith et al. 2006). The corresponding values for our non-low consumers were much lower (mean = 0.019, maximum = 0.17 µg/ml).

A possible source of bias which might, on the other hand, work to exaggerate consumer group differences, concerns the blinding of caffeine abstinence. It may be that knowledge of caffeine abstinence in the caffeine consumers ('I haven't had my morning coffee/caffeine yet') would contribute to lower self-reported alertness and greater sleepiness. Arguably, though, performance is less likely to be affected by this expectancy (cf Haskell et al. 2005) – indeed, such knowledge might even encourage a compensatory increase in effort, which would tend to offset decrements in performance.

Overall then, the present results demonstrate adverse effects of overnight caffeine withdrawal (left hand section of Table 1), which increase in severity as withdrawal continues into the afternoon (compare the results in Fig. 1 for the non-low and medium-high caffeine consumers who received placebo).

Explaining the effects of caffeine and caffeine withdrawal on mental alertness

An important finding of this study is the dissociation of effects of caffeine on mental alertness (I feel mentally alert / attentive / able to concentrate / observant) and sleepiness/wakefulness (I feel sleepy / drowsy / half awake) (Fig. 1a and 1c). Mental alertness was lowest and sleepiness highest in medium-high consumers who received placebo, and the

effect of caffeine was to normalise their mental alertness and sleepiness – medium-high consumers treated with caffeine displayed almost the same levels of mental alertness and sleepiness as non-low consumers treated with placebo. This is fully consistent with withdrawal reversal, and indicates nearly complete tolerance to these effects of caffeine.

Caffeine also reduced sleepiness in non-low consumers, despite their placebo level of sleepiness being lower than that of the medium-high consumers. This reduction in sleepiness was not, however, accompanied by an increase in mental alertness. Why should this be? We suggest that, while reduced sleepiness (increased wakefulness) might have been expected to benefit non-low consumers' mental alertness, this was offset by the increase in anxiety and jitteriness that they experienced when given caffeine (Fig. 1b). This possibility is supported by the regression analyses which showed for non-low consumers a negative relationship between change in anxiety/jitteriness and change in mental alertness after caffeine, which was independent of the relationship between changes in sleepiness and mental alertness. That anxiety and jitteriness will have a negative effect on ability to concentrate and sustain attention, which are components of the mental alertness scale used here, is supported theoretically and empirically. Eysenck et al. (2007), for example, argue that anxiety impairs processing efficiency by decreasing attentional control and increasing attention to threat-related stimuli. In the present study, caffeine did not increase in anxiety/jitteriness in medium-high consumers, presumably because they were tolerant to this effect (Rogers et al. 2010), and for them the decrease in sleepiness after caffeine was accompanied by a related increase in mental alertness.

A summary of the preceding analysis is presented in Fig. 3. Note that the outcomes of tolerance to the effects of caffeine on sleepiness and anxiety/jitteriness in medium-high consumers differ, in that caffeine withdrawal increases sleepiness, but it does not reduce anxiety/jitteriness (probably mainly because there is little room for the already low level of

anxiety/jitteriness to decline further). For non-low consumers Fig. 1 indicates that the magnitude of effects on caffeine on sleepiness and anxiety/jitteriness balance such that there is no net effect on mental alertness. This balance, however, might vary according to the population studied (individual susceptibility to the anxiogenic effects of caffeine differs considerably (Rogers et al. 2010; Yang et al. 2010)), time of day (sleepiness is generally greater mid-afternoon than mid-morning) and dose of caffeine administered. In relation dose, in the present study, participants consumed 100 mg of caffeine followed 90 minutes later by 150 mg. The results reported are for the measures taken during the afternoon after the second dose, although broadly similar effects were apparent for 100 mg. In non-low consumers this dose increased anxiety/jitteriness and decreased sleepiness, although these effects were somewhat smaller than after 100 mg + 150 mg caffeine, and there was a small, non-significant, accompanying increase in mental alertness (data not shown). In contrast, in an as yet unpublished study (Smith, 2011), we observed a significant *reduction* in mental alertness in the late afternoon in non-low caffeine consumers given 250 mg of caffeine in a single, acute dose. It may that at doses of caffeine more representative of individuals' initial exposure to caffeine (Rogers et al. 1995), for example 30-50 mg in tea and cola or in small cups of coffee, that the balance of effects favours increased mental alertness, and that this in turn helps to encourage further consumption. Supporting a balance in favour of a net benefit after lower doses of caffeine, Haskell et al. (2005) found that 75 mg, but not 150 mg, of caffeine significantly decreased ratings of mental fatigue (arguably, the opposite of mental alertness) in non-low caffeine consumers.

In addition to caffeine dose, and possibly time of day and individual differences, another factor contributing to apparent discrepancies in results concerning alerting effects of caffeine is the measurement of alertness. Actually, some findings that show increases in alertness in non-low caffeine consumers probably correspond to an effect on

sleepiness/wakefulness rather than specifically mental alertness. For example, the alerting effect we reported previously in non-low consumers was for data which combined ratings of alertness and tiredness (Rogers et al. 2003), and the similar effect observed by Smith et al. (2006) was for alertness measured on a drowsy–alert bipolar scale.

Faster but not smarter – explaining the effects of caffeine and caffeine withdrawal on performance

The pattern of results for the recognition memory task and the number of errors recorded for the choice reaction time task were strikingly similar to that observed for mental alertness. That is, caffeine did not affect these measures of performance in non-low consumers, and it did not improve performance in medium-high consumers above the level of performance displayed by non-low consumers receiving placebo – rather, it appears that the medium-high consumers receiving placebo were adversely affected by continuing caffeine withdrawal. Therefore, at least from these results, it would seem that caffeine fails to acutely enhance mental performance.

By contrast, caffeine affected tapping performance to the same extent in non-low and medium-high consumers and there was no adverse effect of caffeine withdrawal on this measure (i.e., speed of tapping did not differ between medium-high and non-low consumers given placebo). As the tapping task is primarily a test of motor speed and endurance (see below), with minimal cognitive load, we suggest that the net enhancement of tapping performance represents a motor effect of caffeine.

A third pattern of results was evident for simple and choice reaction times: there was a small, but statistically significant, speeding of reaction time in non-low consumers given caffeine versus their counterparts given placebo, but a larger effect in medium-high consumers who displayed markedly longer reaction times, especially for simple reaction

time, if given placebo. We propose that this pattern can be explained by a net speeding of performance in both non-low and medium-high consumers due to caffeine's motor effect (like the tapping task, the reaction time tasks required a motor response), combined with a withdrawal-related decline in the ability to sustain attention in medium-high consumers. The latter is, of course, evidenced by these participants' low ratings of mental alertness which, as discussed earlier, we suggest is due ultimately to the increase in sleepiness caused by caffeine withdrawal.

This explanation of the effects of caffeine and caffeine withdrawal on reaction times is supported by three further sets of results. First, in medium-high caffeine consumers the effect of caffeine on simple reaction time was predicted by its effects on both tapping performance and mental alertness, whereas for non-low consumers only caffeine's effect on tapping performance predicted its effect on simple reaction time. Second, there was a slowing in simple reaction across block in the medium-high caffeine consumers given placebo. This can be interpreted as a vigilance decrement with time on task due to the caffeine-withdrawal-related decrease in mental alertness. No such slowing with time on task in was observed in the absence of withdrawal (non-low consumers, and medium-high consumers given caffeine). Third, the speeding of simple reaction time performance in non-low consumers was constant across block, indicating that, in contrast to the effect of withdrawal, the motor effect of caffeine did not vary with time on task. Following on from this it is possible to estimate for the simple reaction time task that caffeine withdrawal slowed reaction time by 52 ms. Our calculation, the difference between mean placebo and caffeine reaction times in medium-high consumers minus the difference between mean placebo and caffeine reaction times in non-low consumers (i.e., ((485 – 417) – (437 – 420)), assumes that the purely motor effect of caffeine in these two groups is the same, namely a speeding of 17 ms (represented by the placebo-caffeine difference in non-low consumers) (Fig. 1d). This assumption is supported

by the very similar effect of caffeine on mean tapping speed in non-low and medium-high consumers (6.1 and 6.7 taps per 30 s, respectively) (Fig. 1h). Arguably, simple reaction time displayed by placebo-treated non-low consumers represents 'baseline' performance on this task, as it is unaffected by either caffeine or caffeine withdrawal. Compared with this 'baseline' (mean = 437, SD = 58), a slowing of reaction time of 52 ms due to caffeine withdrawal is a large effect as defined by Cohen (1988).

According to the above analysis of the effects of caffeine and caffeine withdrawal on performance, the difference between the various measures of performance is that the ability to sustain attention affects recognition memory performance and choice reaction time errors, motor speed affects tapping performance, whilst both contribute to determining choice and simple reaction times. In turn, impairment of both speed of information processing and decision making may be implicated in the withdrawal-related decline in sustained attention, as evidenced by, respectively, the slowing of reaction time (i.e., the 52 ms increase in the vigilance-related component of simple reaction time) and the decline in accuracy of performance (increase in recognition memory and choice reaction time errors).

The speeding of tapping performance by caffeine has been observed previously (e.g., Heatherley et al., 2005; Hollingworth 1912; Weiss and Laties 1962; Rogers et al., 2005), and this is consistent with extensive evidence of enhancement by caffeine of physical performance, including an effect on muscular endurance (Warren et al., 2010; Graham, 2001; James et al., 2011; Rogers, 2000). The latter is relevant because, although brief, the tapping task is experienced as fatiguing and tapping rate declines with time on task (data not shown). Central mechanisms are implicated in the motor effects of caffeine (Barthel et al., 2001; Specterman et al., 2005), however also a direct effect on muscle is not ruled out (Warren et al., 2010; James et al., 2011). Notably, the magnitude of the effects of caffeine on physical performance appears to be unrelated to caffeine consumer status (Rogers, 2000; Warren et al.,

2010; James et al., 2011), as was the effect of caffeine on tapping performance in the present study (non-low versus in medium-high consumers) and in an earlier study (acutely versus long-term withdrawn caffeine consumers) (Rogers et al., 2005 – see below).

Therefore, while caffeine clearly does enhance motor performance (faster), as evidenced by faster reaction times and tapping rate after caffeine in both medium-high and non-low caffeine consumers, it does not appear to improve mental performance (it failed to reduce the number of errors made in either the choice reaction time or recognition memory tasks below that of placebo-treated non-low consumers). Caffeine fails to make medium-high caffeine consumers 'smarter' because, due to tolerance to the effects of caffeine on sleepiness/wakefulness, they gain no net increase in mental alertness from their habit. Caffeine, at least in the amounts given in the present study, also fails to increase mental alertness and improve mental performance in non-low consumers. This is because, although caffeine reduces sleepiness in non-low consumers, this potential benefit is offset by an increase in anxiety/jitteriness (Fig. 3).

Non-low caffeine consumers as a model for studying the effects of caffeine – possible sources of bias

A possible problem with our interpretation of the different findings for non-low and medium-high consumers is that these are self-selected groups; that is, perhaps the findings can be explained by individual differences. For example, those who are constitutionally prone to excessive sleepiness in the morning might be more likely to turn to caffeine as a remedy than less sleepy individuals. Against this interpretation is our finding from another study that morning sleepiness (drowsiness) was the same in non-low caffeine consumers and long-term withdrawn medium-high consumers, and raised only after acute caffeine withdrawal (Richardson et al. 1995 – the caffeine consumers were randomised to either acute or long-

term withdrawal). More recently, Sigmon et al. (2009) found the same effect for long-term versus acute caffeine withdrawal for afternoon 'tiredness,' and moreover that caffeine reduced tiredness by an equal degree under long-term and acute caffeine withdrawal. The interpretation of these results is that during extended withdrawal adenosine signalling in (former) caffeine consumers readjusts to eventually match that of non-low consumers (Richardson et al. 1995; James and Rogers, 2005; Juliano and Griffiths, 2004; Sigmon et al. 2009).

For tapping performance we previously found that the effect of caffeine was nearly identical in long-term acutely withdrawn medium-high consumers (again participants were randomised to long-term and acute withdrawal) (Rogers et al., 2005). However, in contrast to sleepiness/drowsiness/tiredness, there was no detrimental effect of acute withdrawal on tapping performance (Rogers et al., 2005). Thus for both sleepiness and tapping, results for non-low consumers closely parallel those for long-term withdrawn medium-high consumers.

In relation to anxiety, it might be that greater susceptibility to the anxiogenic effect of caffeine deters caffeine consumption. However, this does not appear to be the case (Rogers et al. 2010), and in another study we found that a vast majority of non-caffeine consumers selected taste ('I don't like the taste' and 'I prefer other drinks') and concern about health effects ('It's not good for my health'), and not anxiety, jitteriness or tension ('It makes me feel anxious,' etc), as reasons for avoiding tea and coffee (Rogers and Smith 2011).

It appears reasonable, therefore, to conclude that the contrasting effects of caffeine and of caffeine withdrawal we observed in non-low and medium-high caffeine consumers are related to these participants' recent history of caffeine exposure, and not to individual differences pre-dating this exposure.

Final comments and conclusions

An important contribution of the present analysis is the dissociation of sleepiness/wakefulness and mental alertness. In many previous studies on caffeine, including some of ours, alertness has been treated as being on a continuum with drowsiness and sleepiness. However, it seems that subjective alertness, or at least subjective mental alertness, cannot be reduced simply to the absence sleepiness (cf. Shapiro et al. 2006).

In this context, the extent to which tolerance does or does not develop to three behaviourally distinct effects of caffeine appears to explain very well the effects of caffeine and caffeine withdrawal on performance. Specifically, with medium-high consumption there is complete tolerance to the effects of caffeine on daytime sleepiness/wakefulness and on anxiety/jitteriness, but no tolerance to its effects on motor speed/endurance. The increase in sleepiness resulting from withdrawal of caffeine underlies a decrease in mental alertness and impairment of mental performance, all of which are rapidly reversed by caffeine consumption, without it increasing anxiety/jitteriness. Actually, at 10.30 AM after overnight caffeine abstinence, differences in performance between medium-high and non-low consumers, although significant, were fairly small. Therefore, in everyday life medium-high caffeine consumers may largely avoid the adverse effects of caffeine withdrawal by consuming caffeine soon after waking in the morning and intermittently thereafter for the rest of the day (with lower consumption towards evening helping to reduce disruption of sleep) (Smit and Rogers 2007). Nonetheless, reversal of withdrawal effects following the first caffeine-containing drink of the day is sufficient to (negatively) reinforce caffeine consumption habits (Rogers et al., 1995; Rogers and Smith 2011). In contrast to medium-high caffeine consumers, (non-tolerant) non-low consumers experience an increase in anxiety/jitteriness after caffeine which decreases, and in the present study completely offset, any benefit for mental alertness and mental performance arising from reduced sleepiness. There may be contexts in which non-low consumers could make good use of the latter effect,

for example when attempting to remain awake at night during a long-distance drive, or trying to combat the pressure to sleep arising from sleep restriction (Lieberman et al., 2002), but of course to avoid tolerance and withdrawal, consumption would have to be occasional. Finally, non-low and medium-high consumers alike can expect to gain a small advantage for physical performance from caffeine consumption.

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Figure captions

Fig. 1. Results for self-reported sleepiness, anxiety/jitteriness and mental alertness (higher scores indicate higher mental alertness, sleepiness and anxiety/jitteriness; 0-8 point scale) and for task performance (except for the tapping task, higher scores indicate poorer performance). Means which do not share a letter (a, b or c) in common differ significantly, $p < 0.05$ (HSD test). † denotes that there was a significant effect of caffeine versus placebo within the non-low and/or medium-high consumer groups, $p < 0.05$ (ANOVA conducted separately for non-low and medium-high consumers, controlling for pre-treatment baseline score). See text for further statistical details. Participants were required to abstain from caffeine from 7 PM the evening before the test day, and they given caffeine (100 mg then 150 mg) or placebo at 11.15 AM and 12.45 PM, respectively. Data are for tests conducted between 1.45 PM and 3.30 PM.

Fig. 2. Results for simple reaction time task performance by block. There was significant caffeine by consumer status by block interact ($p < 0.02$) (see also Table 1). See caption to Fig. 1 for summary of caffeine abstinence and dosing.

Fig. 3. How the effects of caffeine on sleepiness and anxiety/jitteriness combine to influence mental alertness.

Table 1 Results for Analyses of the Effects of Caffeine Consumer Status at Baseline and for the Effects of Caffeine and Caffeine Consumer Status After Treatment

Measure	Pre-treatment baseline (df = 1,363)	Main and interaction effects of caffeine and consumer status[b] (df = 1,359)		
	Non-low vs medium-high consumers[a]	Caffeine	Consumer status	Caffeine by consumer status
Sleepiness, 0-8 point scale	2.01 ± 0.16 2.35 ± 0.13 $F = 2.90$, $p = .09$	$F = 26.50$, $p < .0001$	$F = 13.58$, $p = .0003$	$F = 1.79$, $P > .1$
Anxiety/Jitteriness, 0-8 point scale	1.12 ± 0.09 1.32 ± 0.08 $F = 2.71$, $p > .1$	$F = 16.78$, $p < .0001$	$F < 1$	$F = 18.66$, $p < .0001$
Mental alertness, 0-8 point scale	5.33 ± 0.13 5.02 ± 0.12 $F = 3.02$, $p = .08$	$F = 10.75$, $p = .001$	$F = 8.89$, $p = .003$	$F = 13.05$, $p = .0003$
Simple reaction time, ms	391 ± 4 402 ± 3 $F = 4.65$, $p = .03$	$F = 26.84$, $p < .0001$	$F = 7.10$, $p = .008$	$F = 10.89$, $p = .001$
Choice reaction time, ms	498 ± 7 511 ± 6 $F = 1.95$, $p > .1$	$F = 10.92$, $p = .001$	$F<1$	$F = 3.30$, $p = .07$
Choice reaction time, number of errors	8.18 ± 0.57 9.92 ± 0.48 $F = 5.43$, $p = .02$	$F=8.87$, $p = .003$	$F = 7.01$, $p = .008$	$F = 2.92$, $p = .09$
Recognition memory, number of errors	13.1 ± 1.1 15.2 ± 0.9 $F = 2.20$, $p = .14$	$F = 3.41$, $p = .065$	$F = 5.18$, $p = .023$	$F = 6.23$, $p = .013$
Tapping, number of taps/30 s	183 ± 2 185 ± 1 $F < 1$	$F = 9.89$, $p = .002$	$F < 1$	$F < 1$

[a]Means and SEs are shown.
[b]See Fig. 1 for means and SEs

Table 2 Predictors of the Effects of Caffeine on Simple Reaction Time Performance and Mental Alertness in Non-low and Medium-high Caffeine Consumers

	Non-low consumers (n=77)	Medium-high consumers (n=106)
Simple reaction time[a]		
Mental alertness[a]	–.14	–.26*
Tapping speed[a]	–.38**	–.27*
Mental alertness[a]		
Sleepiness[a]	–.35**	–.47***
Anxiety/jitteriness[a]	–.38**	–.07

Values in the table are standardized coefficients (β) from standard multiple regression analyses (*p<.01, **p<.001, ***p<.0001).
[a]Data in these analyses were post-caffeine (100 + 150 mg) scores minus baseline scores for participants who received caffeine.

Fig. 1 a-d

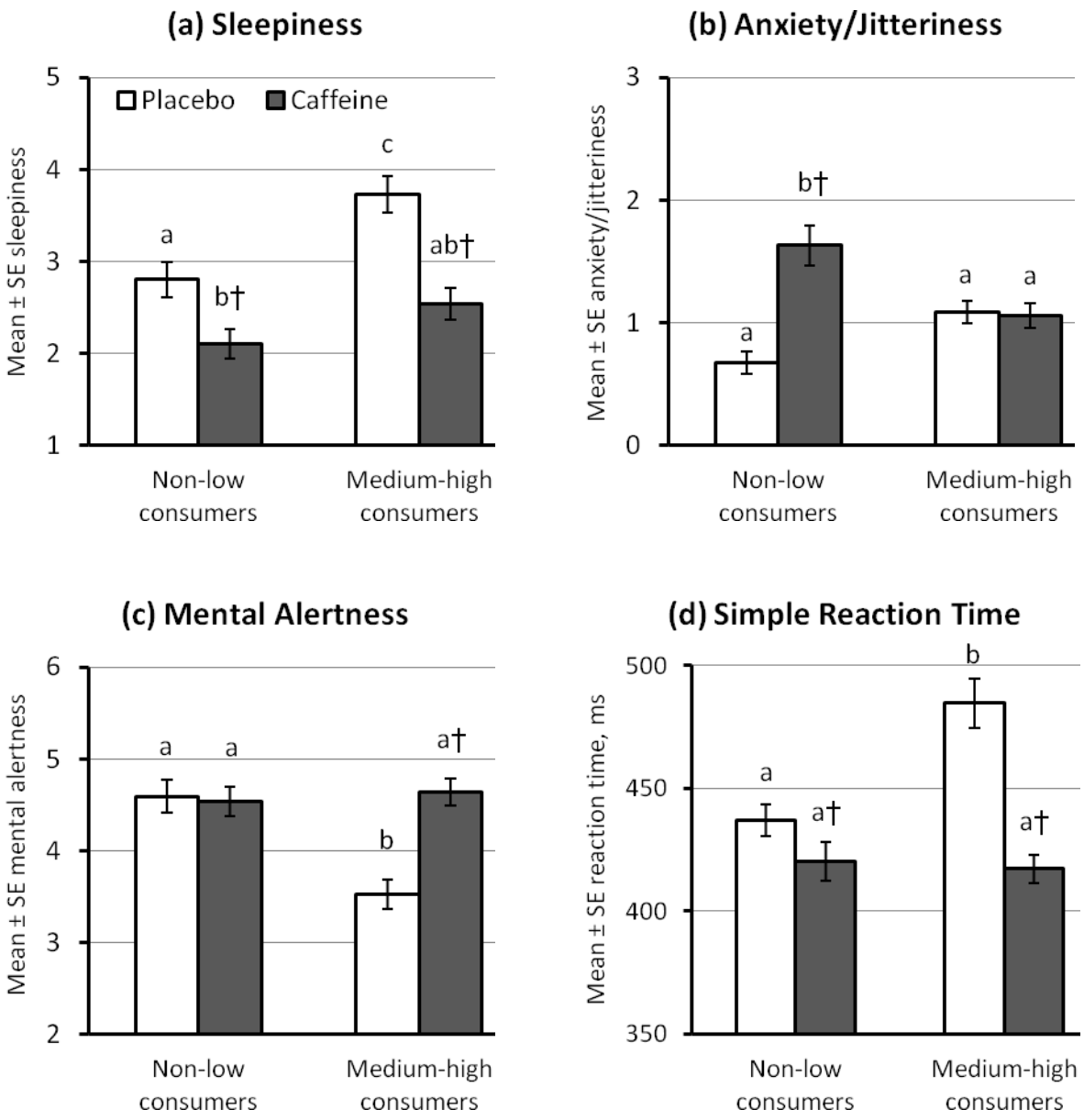
(a) Sleepiness
Placebo
Caffeine
Mean ± SE sleepiness
5
4
3
2
1
a
b†
c
ab†
Non-low consumers
Medium-high consumers
(b) Anxiety/Jitteriness
Mean ± SE anxiety/jitteriness
3
2
1
0
a
b†
a
a
Non-low consumers
Medium-high consumers
(c) Mental Alertness
Mean ± SE mental alertness
6
5
4
3
2
a
a
b
a†
Non-low consumers
Medium-high consumers
(d) Simple Reaction Time
Mean ± SE reaction time, ms
500
450
400
350
a
a†
b
a†
Non-low consumers
Medium-high consumers

Fig. 1 e-h

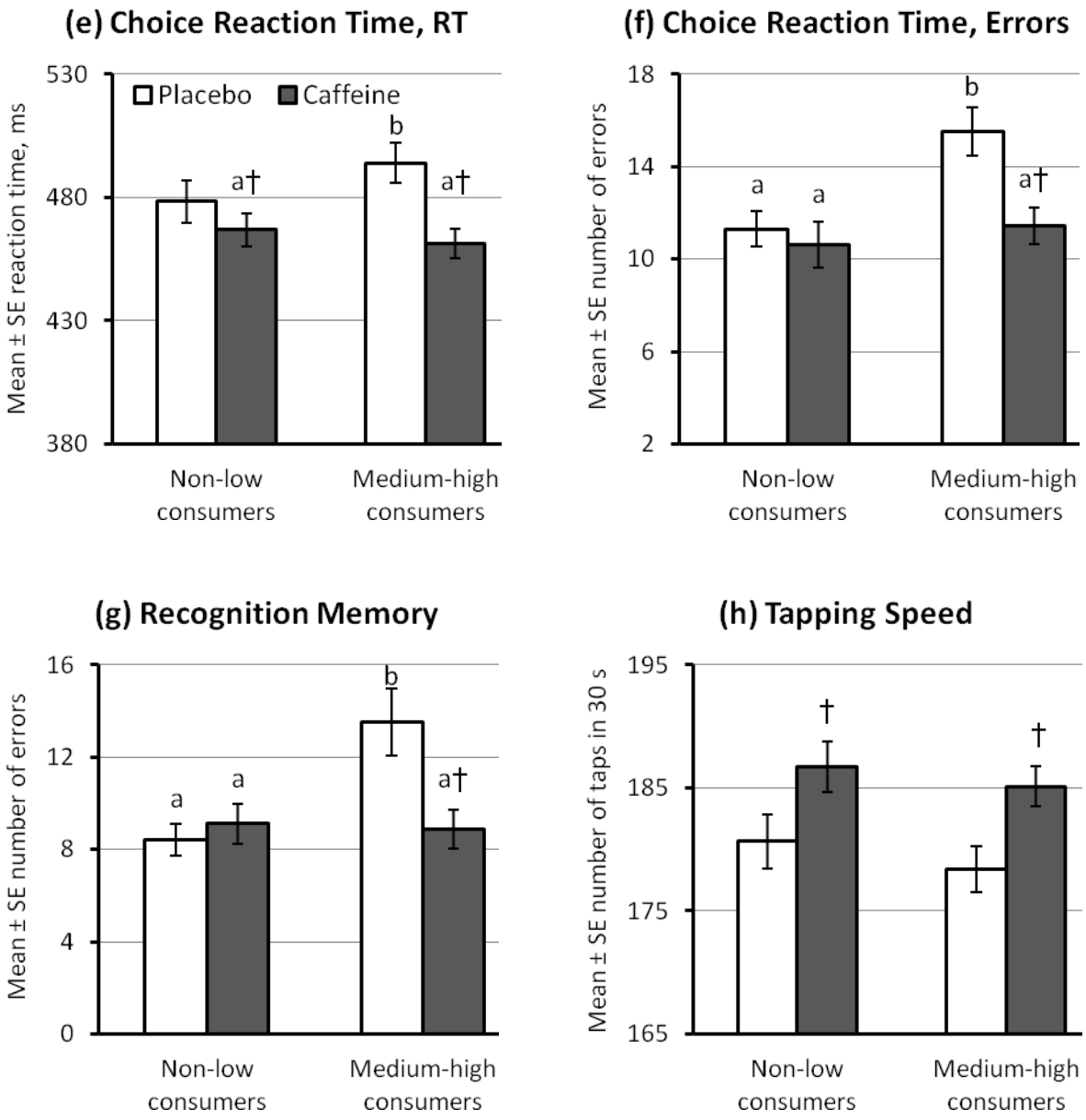
(e) Choice Reaction Time, RT
Mean ± SE reaction time, ms
530
480
430
380
Placebo
Caffeine
a†
b
a†
Non-low consumers
Medium-high consumers
(f) Choice Reaction Time, Errors
Mean ± SE number of errors
18
14
10
6
2
a
a
b
a†
Non-low consumers
Medium-high consumers
(g) Recognition Memory
Mean ± SE number of errors
16
12
8
4
0
a
a
b
a†
Non-low consumers
Medium-high consumers
(h) Tapping Speed
Mean ± SE number of taps in 30 s
195
185
175
165
†
†
Non-low consumers
Medium-high consumers

Fig. 2

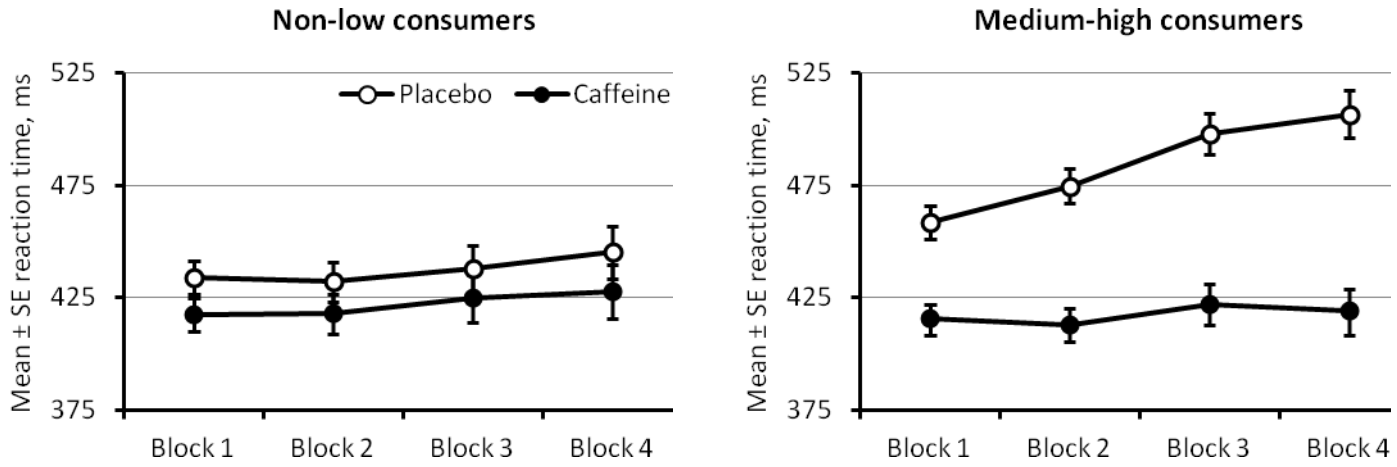
Non-low consumers
Medium-high consumers
Placebo
Caffeine
Mean ± SE reaction time, ms
525
475
425
375
Block 1
Block 2
Block 3
Block 4

Fig. 3

	Sleepiness		Anxiety/Jitteriness		Mental alertness
Non-low consumer, after caffeine	↓	+	↑	=	→
Medium-high consumer, caffeine withdrawn	↑	+	→	=	↓
Medium-high consumer, after caffeine	→	+	→	=	→

↓ decreased, ↑ increased, → normal level