REVIEW

Jack E. James · Peter J. Rogers

Effects of caffeine on performance and mood: withdrawal reversal is the most plausible explanation

Received: 1 April 2005 / Accepted: 23 May 2005 / Published online: 2 July 2005 © Springer-Verlag 2005

Abstract Rationale: Although it is widely believed that caffeine can enhance human performance and mood, the validity of this belief has been questioned, giving rise to debate. The central question is whether superior performance and mood after caffeine represent net benefits, or whether differences between caffeine and control conditions are due to reversal of adverse withdrawal effects. Objectives: To provide a focussed review of relevant experimental studies with the aim of clarifying current understanding regarding the effects of caffeine on human performance and mood. Methods: To avoid the shortcomings of standard placebo-controlled studies, which are ambiguous due to failure to control for the confounding influence of withdrawal reversal, three main experimental approaches have been employed: studies that compare consumers and low/non-consumers, pre-treatment and ad lib consumption studies, and long-term withdrawal studies. Results: Of the three approaches, only long-term withdrawal studies are capable of unambiguously revealing the net effects of caffeine. Overall, there is little evidence of caffeine having beneficial effects on performance or mood under conditions of long-term caffeine use vs abstinence. Although modest acute effects may occur following initial use, tolerance to these effects appears to develop in the context of habitual use of the drug. Conclusions: Appropriately controlled studies show that the effects of caffeine on performance and mood, widely perceived to be net beneficial psychostimulant effects, are almost wholly attributable to reversal of adverse withdrawal effects associated with short periods of abstinence from the drug.

J. E. James (⊠)

Department of Psychology, National University of Ireland, Galway, Ireland

e-mail: j.james@nuigalway.ie Tel.: +353-91-512016 Fax: +353-91-521355

P. J. Rogers

Department of Experimental Psychology, University of Bristol, Bristol, BS8 1TN, UK

Keywords Caffeine · Performance · Mood · Sleep restriction · Withdrawal reversal · Fatigue · Alertness

Introduction

Caffeine is the most widely consumed psychoactive substance in history (James 1997). Its widespread use may be due in part to the perception that oral ingestion of the drug enhances performance and mood. However, the validity of the belief that caffeine can enhance human performance and mood has been questioned, giving rise to debate (James 1994a, 1995, 1997; Smith 1995, 2002; Warburton 1995; Rogers and Dernoncourt 1998; Warburton et al. 2001). The kernel of the debate is the claim that a large number of empirical studies, conducted over several decades, contained a flaw arising from the uncritical adoption of the standard placebo-controlled drug trial (James 1994a). The typical format in such studies has involved measurement of performance and mood in "normal" volunteers (e.g. college students) before and after doubleblind administration of caffeine and placebo. Compared to baseline and placebo, improved levels of performance and mood have often been observed post caffeine, leading to the conclusion that caffeine enhances performance and mood. However, a critical appraisal of this standard design shows that the findings it has yielded are, at best, ambiguous. This paper provides a focussed review of the relevant literature with the aim of clarifying current confusion and misunderstanding in relation to the effects of caffeine on human performance and mood.

When comparing studies of the effects of caffeine on performance, it is important to recognise that measures of performance have varied greatly. These have ranged from relatively "simple" psychomotor activities, such as hand steadiness and manual dexterity, to more "complex" cognitive activities, such as mental arithmetic and memory. One trend evident in the literature is that complex higher-level cognitive processes have generally been reported to be less responsive to caffeine than more simple, repetitive and prolonged psychomotor activities. While not ignoring

task-specific differences in responding, the particular concern of this review is the more general question of whether caffeine has indeed been shown to enhance performance, irrespective of the task involved. Another theme, to which we return below, is the suggestion that caffeine has greater potential to enhance performance in persons who are fatigued as opposed to rested. In this context, self-reported "alertness" has frequently been a concomitant interest. Indeed, although caffeine studies have examined a wide range of mood states, the dimension of alertness has been particularly prominent. Although interest in this dimension seems appropriate in the context of the presumed "stimulant" properties of caffeine, our examination suggests that the effects of caffeine on subjective alertness are more complex than has generally been assumed.

Confounding due to reversal of withdrawal effects

It is standard practice in placebo-controlled studies, for example, of therapeutic drugs, to withhold the drug in question for a period prior to testing for effects, because of the importance of ensuring that all participants are equivalent in systemic drug levels at time of testing. Such control procedures are especially pertinent to the assessment of caffeine effects, because the drug is so widely used. Caffeine is usually consumed in separate portions throughout the day, with fewer portions consumed later in the day, followed by overnight abstinence. With the half-life of caffeine in healthy adults being approximately 6 h (Pfeifer and Notari 1988), typical overnight abstinence of 10-14 h results in substantial elimination of systemic caffeine by early morning (Lelo et al. 1986a,b). Regarding the use of the placebo-controlled paradigm in caffeine studies, researchers frequently make use of naturally occurring overnight abstinence by asking participants to forgo their usual morning caffeine beverage prior to laboratory testing. What has not been fully appreciated until recently is that, having avoided caffeine since the evening before, study participants may be entering the early stages of caffeine withdrawal by the time they are tested in the laboratory. Accordingly, although generally presented as investigations of the effects of caffeine compared to caffeine-free controls, typical studies of caffeine effects on performance and mood can equally be conceptualized as studies of the effects of caffeine withdrawal, and sometimes have been conceptualized that way (e.g. Mitchell et al. 1995; Streufert et al. 1995; Phillips-Bute and Lane 1998; Watson et al. 2000).

It follows from the above that the key question in this debate is whether superior performance and improved mood after caffeine ingestion represent net benefits, or whether differences between caffeine and control conditions are due to reversal of the adverse withdrawal effects that accompany brief periods of abstinence. Indeed, a third possibility exists, namely, that observed "benefits" are a combination of net effects and withdrawal reversal. Habitual use of caffeine produces physical dependence, evidenced by the appearance of withdrawal symptoms following periods of abstinence (e.g. Griffiths et al. 2003). In support

of the withdrawal reversal hypothesis, there is extensive direct evidence showing that caffeine withdrawal has a wide range of adverse effects. The most comprehensive review of the relevant literature published to date concluded that withdrawal reliably produces the following effects: "headache, tiredness/fatigue, decreased energy/activeness, decreased contentedness/well-being, depressed mood, difficulty concentrating, irritability and foggy/not clearheaded" (Juliano and Griffiths 2004).

It has been suggested that studies of caffeine withdrawal effects may have been confounded by participant expectancies (Smith 2002). However, that suggestion lacks support, as control of participant expectancies has been a feature of much of the relevant empirical research (e.g. Richardson et al. 1995; Garrett and Griffiths 1998; James 1998; Rogers et al. 1998, 2005; James and Gregg 2004a; James et al. 2005; Tinley et al. 2003), leading Juliano and Griffiths (2004) to conclude that the available evidence "overwhelmingly" supports withdrawal effects being pharmacological rather than expectancy based. Moreover, the time course of withdrawal is within the timeframe of typical overnight abstinence (10–14 h), such that initial abstinence effects are likely to have begun by the time the first caffeine beverage of the day is ingested (whether self- or experimenter-administered). There is good evidence of performance and mood being adversely affected by caffeine withdrawal (e.g. James et al. 1988; Richardson et al. 1995; Rogers et al. 2003, 2005), and evidence has long existed that withdrawal-induced dysphoric effects are relieved when caffeine is re-ingested (Griffiths et al. 2003; Juliano and Griffiths 2004).

Attempts to control for the confounding influence of caffeine withdrawal

Considering the limitations of the typical drug-challenge protocol for clarifying the effects of caffeine on human performance and mood, three main alternative empirical paradigms have been proposed (James 1997). The three approaches, each of which employs a different method for dealing with the problem of confounding due to caffeine withdrawal, may be succinctly described as studies that compare consumers and low/non-consumers, pre-treatment and ad lib consumption studies, and long-term withdrawal studies.

Studies comparing consumers and low/non-consumers

In this approach, caffeine is administered to low- or non-consumer "naïve" participants for whom the likelihood of caffeine withdrawal would be lessened or removed. However, inasmuch as more than 80% of the population consumes one or more caffeine beverages daily (James 1997), low use is atypical. Considering the presence of caffeine in chocolate and other non-beverage foodstuffs, as well as some medications, complete non-use of caffeine may be close to non-existent. Importantly, then, be-

cause persons who consume little or no caffeine represent a small self-selected minority, the generality of any effects they might show is open to question. Their low use of caffeine might not only make them unrepresentative, but their reaction to caffeine might also be atypical. In particular, a high proportion of infrequent consumers may have adverse reactions to caffeine (e.g. Alsense et al. 2003), and this may explain their low use of the drug.

Shortcomings in the logic of studies that seek to establish the net effects of caffeine by comparing consumers with low/non-consumers are illustrated in a recent study by Haskell et al. (2005). They found few differences in performance and mood between caffeine consumers who were abstinent for at least 12 h and habitual low consumers, a result the authors took as evidence against withdrawal reversal in consumers. In reality, the results they reported permit no definite conclusions about withdrawal reversal, because the consumers and low-consumers studied represent two distinct self-selected groups. Difference or absence of difference in performance and mood between the two groups could be due to an essentially unlimited number of uncontrolled and unknown characteristics of the respective groups. Indeed, Haskell et al. (2005) infer from their results that caffeine abstinence in habitual consumers produces no withdrawal effects, an inference that underscores the illogic of believing that the net effects of caffeine can be established by comparing consumers with low/non-consumers. Evidence of caffeine withdrawal effects is extensive, unequivocal and essentially conclusive (Juliano and Griffiths 2004).

Moreover, other studies that also compared the effects of caffeine on performance and mood in overnight-withdrawn consumers and low/non-consumers have yielded results different from those reported by Haskell et al. (2005). In particular, following placebo, performance and mood have been found to be worse in withdrawn consumers than in low/non-consumers, whereas caffeine has been found to improve performance and mood in consumers, up to but not above levels for low/non-consumers, suggesting reversal of withdrawal effects (Goldstein et al. 1969; Bruce et al. 1991; Richardson et al. 1995; Rogers et al. 1995, 2003; Heatherley et al. 2005a). Furthermore, these same studies found caffeine to have some adverse effects in low/ non-consumers, while providing little or no net benefit to either consumers or low/non-consumers. At the same time, Haskell et al. (2005) reported significant, although modest, improvements in low/non-consumers' performance and mood after caffeine. This finding, however, does not contradict withdrawal reversal as the main process underlying the effects of habitual caffeine consumption. The modest acute effects reported by Haskell et al.(2005) are likely to be subject to the development of tolerance with continued caffeine use (see below).

Pre-treatment and ad lib consumption studies

In pre-treatment and ad lib consumption studies, participants are "pre-treated" with caffeine so that they might be

"minimally", or not at all, caffeine deprived when tested for performance and mood effects after a subsequent dose of caffeine. Although employed in several recent studies, this approach (as a test of withdrawal reversal vs net benefit) is inherently flawed. Because caffeine consumption patterns and rate of caffeine metabolism vary between individuals, difficulties exist in estimating the precise amount of pre-treatment caffeine needed to ensure uniform and complete removal of caffeine withdrawal effects from one individual to the next. Perhaps reflecting these difficulties, the approach has produced inconsistent findings. Several studies have reported enhanced performance and mood after a second or subsequent caffeine dose following pre-treatment (Warburton 1995; Warburton et al. 2001; Christopher et al. 2005; van Duinen et al. 2005), whereas others failed to observe any enhancement of either performance or mood after caffeine was ingested within less than 6-8 h following pre-treatment (Robelin and Rogers 1998; Yeomans et al. 2002; Heatherley et al. 2005b). It is noteworthy that in the studies reporting positive results, participants were relied upon to self-administer the pretreatment dose(s) while unsupervised. The problem of lack of supervision has been compounded by the use of varying and imprecise instructions. For example, Warburton et al. (2001) told participants "they could consume their normal quantities (of caffeine) during the day", whereas van Duinen et al. (2005) informed participants they "were allowed to consume one cup of coffee" prior to testing. As pointed out by Heatherley et al. (2005b), allowing participants to assume responsibility for the pre-treatment dose is a less reliable method than administering pre-treatment under supervision in the laboratory setting. In contrast to unsupervised administration, studies in which pre-treatment was administered under strict supervision in the laboratory have reported no caffeine effects following a second dose unless the interval between the two doses exceeded 6 h (Robelin and Rogers 1998; Yeomans et al. 2002; Heatherley et al. 2005b).

Acknowledging the shortcomings of unsupervised pretreatment, Christopher et al. (2005) collected saliva samples for subsequent analysis as a means of verification. Thus, although participants were unsupervised while consuming "their normal amount of caffeine over the course of the day", two saliva samples were collected from each, one in the morning "before work" and another in the late afternoon "after work". Performance and mood were tested after work, and improvements in performance and mood were attributed to a caffeine dose administered in the laboratory (after the "after work" saliva sample was taken). However, inspection of the reported saliva results shows that the attempt to monitor caffeine intake during the day was not successful. The saliva caffeine levels reported by Christopher et al. (2005) (Table 1) of 4.35 µg/ml before work and 4.45 µg/ml after work for the caffeine condition and 3.44 µg/ml before work and 4.68 µg/ml after work for the placebo condition are unlikely to be reliable estimates. Previous research shows that typical patterns of caffeine consumption result in a progressive increase in systemic caffeine levels throughout the course of the day, peaking in

the late afternoon or early evening (Lelo et al. 1986a,b; James et al. 1988, 2005; Pfeifer and Notari 1988; James and Gregg 2004a). The Christopher et al. (2005) results show no such pattern. In the caffeine condition, the beforeand after-work levels are almost identical, whereas in the placebo condition, the mean after-work level is only marginally higher than the before-work level.

In particular, the saliva caffeine results representing before-work levels are too high to reflect normal dietary patterns of caffeine consumption (e.g. Pfeifer and Notari 1988). Moreover, there is marked inconsistency between the reported saliva caffeine levels and results shown for self-reported caffeine intake in the same study (Christopher et al. 2005; Fig. 1). The self-reported intake levels show a fairly typical pattern of intermittent caffeine intake throughout the day evidenced by a cumulative increase in milligram level. The mean before-work self-reported caffeine intake was in the region of 50-60 mg, an amount which in normal participants (with healthy liver function) could not possibly produce before-work caffeine saliva levels in excess of the 3–4 µg/ml reported by Christopher et al. (2005) (Table 1). Thus, it may be concluded that either the saliva tests were unreliable (and do not serve to validate the pre-treatment dosing procedure), or participants displayed highly atypical patterns of caffeine consumption (and therefore the results are not generalisable).

Regarding the experiment proper, Christopher et al. (2005) stated that special care was taken to ensure the measures of performance and mood they selected and included only tests that previous studies had shown to be sensitive to caffeine. A total of nine performance tests were selected on that basis, consisting of three measures of focussed attention (mean reaction time, number of lapses of attention, speed of encoding), three measures of categoric search (mean reaction time, lapses of attention, speed of encoding), one measure of simple reaction time and two measures of repeated digits (mean reaction time, total number of hits). Mood was assessed using scales that yielded scores on three factors: alertness, anxiety and hedonic tone. Having consumed caffeine ad lib throughout the day, participants presented at the laboratory "after work", when baseline measurements were taken, followed by caffeine 2 mg/kg or placebo, followed by further testing.

In all, 15 pair-wise statistical tests were conducted, consisting of baseline vs post-caffeine/placebo comparisons for the nine tests of performance and six comparisons for mood in which baseline levels on the three factors were compared with levels both before and after the battery of performance tests. Of these 15 statistical tests, one performance test yielded a significant result at the p < 0.05level, and one was significant at the p < 0.05 level for mood (Christopher et al. 2005; Table 2). Two further comparisons were deemed to be significant after applying one-tailed tests of significance at the p < 0.05 level. However, considering the care the researchers had taken in choosing the measures of performance and mood, it follows that significant results were expected for all or most of the 15 comparisons. Nonetheless, only 4 out of 15 tests were found to be significant at the lowest accepted level of statistical significance. Importantly, it is evident that none of these significant results would survive a Bonferroni correction to adjust significance levels in line with the number of multiple tests performed. Accordingly, a generous interpretation of the results might suggest marginal enhancement of performance and mood when caffeine was ingested in the late afternoon following intermittent consumption during the day, whereas a more rigorous approach to statistical testing would indicate no substantive net effect of caffeine. In summary, considering the unsuccessful attempt to use saliva sampling to monitor pre-treatment systemic caffeine levels, the Christopher et al. (2005) study may be added to previous studies that also reported beneficial effects when caffeine pre-treatment was unsupervised. This is in contrast to other studies that controlled pre-treatment exposure to caffeine (e.g. by administering the pre-treatment dose under supervision in the laboratory), wherein no enhancement was found for either performance or mood following a subsequent caffeine dose administered less than 6–8 h later (Heatherley et al. 2005b; Robelin and Rogers 1998; Yeomans et al. 2002).

In any case, as mentioned at the beginning of this section, no matter how carefully experiments using this approach are done, they cannot with certainty distinguish between withdrawal reversal and net beneficial effects. This is because there is no way of knowing that the pretreatment dose of caffeine had both fully removed and prevented the reappearance of withdrawal effects at the point when the subsequent dose of caffeine was given. In fact, these are essentially dose-response studies, in that they administer one or more doses of caffeine followed by caffeine or placebo, resulting in different systemic concentrations of caffeine at time of testing. Overall, the findings are consistent with a rather flat dose–response relationship for effects of caffeine on performance and mood within the range of caffeine levels contained in drinks such as coffee, tea and cola. Indeed, in this respect, the evidence from these "repeated-dosing" studies (i.e. Robelin and Rogers 1998; Yeomans et al. 2002; Heatherley et al. 2005b; and see also Yeomans et al. 1998) converges with findings from more "conventional" dose-response studies (e.g. Lieberman et al. 1987; Smit and Rogers 2000).

The study by Heatherley et al. (2005b) shows that after a cup-of-coffee equivalent dose of caffeine in overnightwithdrawn consumers, it takes between 6 and 8 h for systemic caffeine levels to fall below a "threshold" at which alertness and performance are again affected by caffeine relative to placebo. Although the threshold concentration is low relative to peak systemic caffeine levels achieved when several cups of coffee or tea are consumed daily, sub-threshold levels are achieved during overnight caffeine abstinence. This analysis is consistent with the observed elimination half-life of caffeine of about 5 h (Pfeifer and Notari 1988), and the flat dose-response relationship for the effects of caffeine on performance (Lieberman et al. 1987; Smit and Rogers 2000). In studies in which pretreatment exposure to caffeine was self-administered, and therefore not tightly controlled, it may be that at least some participants were more than 6 h caffeine deprived prior to arrival in the laboratory for subsequent treatment and testing. For example, the marginal effects of caffeine reported by Christopher et al. (2005) are consistent with a small proportion of participants (>6 h caffeine deprived) responding to caffeine with improved mood and performance, with the remainder (<6 h deprived) showing effects of caffeine no different from those of placebo.

Long-term withdrawal studies

In recognition of the inherent limitations of the two approaches considered above, a third strategy has been advocated as the preferred approach for establishing the net effects of caffeine on performance and mood uncontaminated by withdrawal reversal (James 1997, 2003). This approach recognises the need for study designs that permit direct within-subject comparisons of the effects of sustained periods of caffeine use and abstinence in persons who are habitual consumers. Studies of this kind are particularly demanding on participants and research resources, because of the requirement that participants be tested repeatedly over protracted time periods when participants are with and without caffeine. Investment in this approach. however, is justified in light of the high level of consistency in reported findings and the general conclusions that may be drawn, not only in relation to caffeine effects on performance and mood but also in relation to caffeine-induced physiological effects (James 2004; James and Gregg 2004b).

Strong support for the withdrawal reversal hypothesis is to be found in studies in which performance and mood have been compared in the same participants who have experienced prolonged periods of caffeine and placebo, respectively, with the aim of effectively "washing out" the effects of caffeine tolerance and withdrawal. Taking the core features of the traditional drug-challenge paradigm, with its attendant strengths of double blinding and placebo control, James (1998) extended the protocol to include four consecutive 1-week periods, with a strictly prescribed and biologically verified regimen of caffeine intake for every day of each week. During caffeine phases, participants ingested the approximate equivalent of one cup of coffee three times daily, thereby simulating the typical population pattern of caffeine consumption. The protocol employed six consecutive days of placebo/caffeine intake to ensure stability of responding before "challenging" participants on the seventh day of each alternating 1-week period. The 1week timeframe was chosen on the basis of findings from previous research. Although tolerance has been confirmed infrequently in human studies, when it has been observed (e.g. partial tolerance of caffeine-induced increases in blood pressure), it has generally be found to plateau within 3 to 5 days of continuous use (Robertson et al. 1981; Denaro et al. 1991; James 1994b). Withdrawal effects have been examined more extensively, and have been found to abate within a similar timeframe (i.e. 3-5 days and not more than a week) (e.g. Griffiths et al. 1986; Hughes et al. 1993). The use of alternating periods of caffeine exposure and abstinence by James (1998) meant that the separate acute and chronic effects of caffeine could be examined and compared in one experiment. Overnight caffeine abstinence was found to have detrimental effects on performance and mood, and these effects were removed when caffeine was re-ingested (restoration due to reversal of withdrawal effects).

Most importantly, James (1998) found no evidence of caffeine having any beneficial effect on performance or mood under conditions of sustained caffeine use vs sustained abstinence (i.e. withdrawal washout). Other studies performing similar comparisons have reported similar results in relation to caffeine reinforcement (Garrett and Griffiths 1998; Tinley et al. 2003), as well for effects on performance and/or mood (Richardson et al. 1995; Garrett and Griffiths 1998; Rogers et al. 1998, 2005; James and Gregg 2004a; James et al. 2005). Whereas these studies suggest that caffeine has little or no net benefits for performance and mood, several studies have reported acute caffeine effects on mood when the drug was ingested after long-term abstinence (Silverman and Griffiths 1992; Mumford et al. 1994; Silverman et al. 1994; James 1998). At the same time, it is evident from the James (1998) study that the magnitude of any such acute effects are modest compared to the effects accounted for by withdrawal reversal. Moreover, it appears that even these effects, which would qualify as acute net effects, undergo tolerance in the context of habitual caffeine use (Richardson et al. 1995; James 1998; Garrett and Griffiths 1998; Rogers et al. 1998, 2005; James and Gregg 2004a; James et al. 2005). That is, short-term withdrawal (e.g. overnight) has marked detrimental effects on mood that are reversed when caffeine is next ingested (e.g. shortly after waking in the morning). Conversely, ingesting caffeine after long-term abstinence may have modest positive effects on mood, but tolerance to these effects occurs with ongoing use of the drug.

Whereas acute effects, not attributable to withdrawal reversal, are evident but modest for mood, any acute benefits in performance seem even less consequential. Although Silverman et al. (1994) reported a decrease in number of misses on a vigilance task when caffeine was ingested after long-term abstinence, no significant performance effects were observed when caffeine was ingested under similar conditions in another study by the same group (Silverman and Griffiths 1992). In addition, James (1998) and Rogers et al. (1998, 2005) found no evidence of enhanced performance when caffeine was ingested acutely after long-term abstinence, and no evidence of enhancement after habitual use for either a battery of performance tasks (James et al. 2005) or prolonged vigilance (James 1998; James et al. 2005). Actually, the most reliable effect of caffeine on performance is its ability to increase tremor (Gilliland and Bullock 1984), particularly as measured by decreased hand steadiness (e.g. Chait and Griffiths 1983; James 1990; Richardson et al. 1995; Heatherley et al. 2005b). It should be noted, moreover, that increased tremor is a genuine net effect of caffeine, because acute caffeine withdrawal does not improve hand steadiness above chronically caffeine-free levels (Rogers et al. 2005). Indeed, caffeine-induced increases in "psychomotor agitation" (Gilliland and Bullock 1984) may help to explain the mismatch that has been observed between the apparent alerting effect of caffeine and the absence of net benefits on performance (Rogers et al. 2003). It appears likely that the increased "alertness" that has been reported could be a misinterpretation of other subjective effects, such as increased "jitteriness" (e.g. Goldstein et al. 1969; Richardson et al. 1995; Silverman and Griffiths 1992; Silverman et al. 1994).

Although this review has focussed on caffeine effects in non-fatigued persons, researchers have long been interested in the potential of caffeine to counter the fatiguing effects of lack or loss of sleep. Indeed, it has been claimed that caffeine is especially potent in this regard. For example, Reyner and Horne (2002), assessing the "beneficial" effects of a well-known brand of caffeine "energy" drink (Red Bull), administered it double blind to 12 sleeprestricted young adults, whose performance was tested on a driving simulation task. The results were interpreted as showing that caffeine significantly improved performance (i.e. reduced the frequency of driving "incidents" such as lane drift). However, participants were moderate consumers ("two to four cups daily") and all presented for testing in a state of caffeine deprivation. Indeed, participants were instructed to abstain from caffeine after 6.00 p.m. the evening before testing, which began at approximately 2.00 p.m. in the afternoon of the test day. That is, at the beginning of testing, participants had been deprived of caffeine for a minimum of 20 h, well within the time period when pronounced adverse withdrawal effects occur. Accordingly, in contrast to net benefits, this study, like many that preceded it, can also be explained in terms of withdrawal reversal. This conclusion is supported by the findings of recent studies of the effects of caffeine on performance and mood in persons who have been sleep restricted.

Using a version of the design employed by James (1998), James et al. (2005) examined the effects of dietary caffeine on performance and mood in 96 healthy volunteers who alternated weekly between placebo and caffeine, while either rested or deprived of more than 50% of their usual nighttime sleep on the evening before testing. Performance involved either a single task requiring sustained vigilance or a varied battery of brief psychomotor and cognitive tasks. Caffeine had no significant net enhancing effects for either performance or mood when participants were rested, and produced no net restorative effects when performance and mood were degraded by sleep restriction. On the contrary, using a similar design, James and Gregg (2004a) found evidence of adverse effects of caffeine on mood during both conditions of rest and sleep restriction.

Similarly, after controlling for caffeine withdrawal effects, Rogers et al. (2005) found that cognitive performance was unimproved by caffeine in the sleep-restricted state. Acute (overnight) caffeine withdrawal was found to impair performance on tasks requiring sustained attention, and subsequent caffeine intake merely prevented further

deterioration in performance. In contrast, the significantly better levels of performance on the same tasks shown by long-term (3 weeks) withdrawn participants were unaffected by caffeine. Additionally, acute caffeine withdrawal had a variety of negative effects on mood. Overall, rather than benefits, these recent studies (James 1998; Rogers et al. 1998, 2005; James and Gregg 2004a; James et al. 2005) confirm the presence of modest net adverse effects of caffeine on a variety of indices of performance and mood. Thus, findings from studies in which withdrawal reversal was controlled do not support the use of caffeine as a general performance enhancer, and especially not with the aim of reducing accidents (e.g. amongst drivers). Rather than decrease risk, there is the potential for dietary caffeine to increase risk of accident due to sleepiness being exacerbated during periods of the day when consumers are relatively caffeine deprived.

Conclusions

Although caffeine is widely perceived to have beneficial psychostimulant effects, appropriately controlled studies show that its apparent beneficial effects on performance and mood are almost wholly attributable to reversal of the withdrawal effects that occur after fairly short periods of abstinence (e.g. overnight). That is, the caffeine-induced improvements in performance and mood often perceived by consumers do not represent net benefits, but rather reversal of the performance-degrading effects of caffeine withdrawal. It appears from a minority of low/non-consumer and long-term abstinence studies that there may be some modest improvement in mood, and perhaps performance, as an acute effect of caffeine when ingested in the absence of withdrawal. However, these effects are small and inconsequential compared with the effects attributable to withdrawal reversal. Crucially, these modest acute net effects also seem to be subject to the development of tolerance when caffeine is consumed habitually.

Furthermore, when performance and mood are degraded by loss of sleep, caffeine has not been found to have any beneficial restorative effects above and beyond those attributable to reversal of withdrawal. Therefore, although positive reinforcing effects of caffeine (e.g. modest mood enhancement) may contribute to some extent to the initiation of caffeine consumption, those effects are not a feature of regular, everyday consumption. Rather, habitual caffeine use is maintained by withdrawal reversal (negative reinforcement) with no net enhancement of functioning (Garrett and Griffiths 1998; Rogers et al. 1995; Tinley et al. 2003). In light of these conclusions, future research into the effects of caffeine on performance and mood must include effective experimental controls against confounding due to reversal of withdrawal effects. Failure to control adequately for confounding by withdrawal reversal will exacerbate the confusion and misunderstanding that currently exists in relation to the effects of this ubiquitously consumed substance.

References

- Alsense K, Deckert J, Sand P, de Wit H (2003) Association between A_{2A} receptor gene polymorphisms and caffeine-induced anxiety. Neuropsychopharmacology 28:1694–1702
- Bruce M, Scott N, Shine P, Lader M (1991) Caffeine withdrawal: a contract of withdrawal symptoms in normal subjects who have abstained from caffeine for 24 hours and for 7 days. J Psychopharmacol 5:129–134
- Chait LD, Griffiths RR (1983) Effects of caffeine on cigarette smoking and subjective response. Clin Pharmacol Ther 34: 612–622
- Christopher G, Sutherland D, Smith A (2005) Effects of caffeine in non-withdrawn volunteers. Hum Psychopharmacol Clin Exp 20:47–53
- Denaro CP, Brown CR, Jacob PI, Benowitz NL (1991) Effects of caffeine with repeated dosing. Eur J Clin Pharmacol 40:273–278
- Garrett BE, Griffiths RR (1998) Physical dependence increases the relative reinforcing effects of caffeine versus placebo. Psychopharmacology 139:195–202
- Gilliland K, Bullock W (1984) Caffeine: a potential drug of abuse. Haworth, New York
- Goldstein A, Kaizer S, Whitby O (1969) Psychotropic effects of caffeine in man. IV. Quantitative and qualitative differences associated with habituation to coffee. Clin Pharmacol Ther 10: 489–497
- Griffiths RR, Bigelow GE, Liebson IA (1986) Human coffee drinking: reinforcing and physical dependence producing effects of caffeine. J Pharmacol Exp Ther 239:416–425
- Griffiths RR, Juliano LM, Chausmer AL (2003) Caffeine: pharmacology and clinical effects. In: Graham AW, Schultz TK, Mayo-Smith MF, Ries RK, Wilford BB (eds) Principles of addiction medicine, 3rd edn. American Society of Addiction Medicine, Chevy Chase, MD, pp 134–193
- Haskell CF, Kennedy DO, Wesnes KA, Scholey AB (2005) Cognitive and modd improvements of caffeine in habitual consumers and habitual non-consumers of caffeine. Psychopharmacology (in press)
- Heatherley SV, Hancock KMF, Rogers PJ (2005a) Psychostimulant and other effects of caffeine in 9- to 11-year-old children. J Child Psychol Psychiatry (in press)
- Heatherley SV, Hayward RC, Seers HE, Rogers PJ (2005b) Cognitive and psychomotor performance, mood, and pressor effects of caffeine after 4, 6 and 8 h caffeine abstinence. Psychopharmacology 178:461–470
- Hughes JR, Oliveto AH, Bickel WK, Higgins ST, Badger GJ (1993) Caffeine self-administration and withdrawal: incidence, individual differences and interrelationships. Drug Alcohol Depend 32:239–246
- James JE (1990) The influence of user status and anxious disposition on the hypertensive effects of caffeine. Int J Psychophysiol 10:171–179
- James JE (1994a) Does caffeine enhance or merely restore degraded psychomotor performance? Neuropsychobiology 30:124–125
- James JE (1994b) Psychophysiological effects of habitual caffeine consumption. Int J Behav Med 1:247–263
- James JE (1995) Caffeine and psychomotor performance revisited. Neuropsychobiology 31:202–203
- James JE (1997) Understanding caffeine: a biobehavioral analysis. Sage, Thousand Oaks, CA
- James JE (1998) Acute and chronic effects of caffeine on performance, mood, headache, and sleep. Neuropsychobiology 38: 32–41
- James JE (2003) Caffeine, mental performance and mood. In: Watson D (ed) Performance functional foods. Woodhead, London, pp 168–194
- James JE (2004) A critical review of dietary caffeine and blood pressure: a relationship that should be taken more seriously. Psychosom Med 66:31–71

- James JE, Gregg ME (2004a) Effects of dietary caffeine on mood when rested and sleep restricted. Hum Psychopharmacol Clin Exp 19:333–341
- James JE, Gregg ME (2004b) Hemodynamic effects of dietary caffeine, sleep restriction, and laboratory stress. Psychophysiol 41: 914–923
- James JE, Paull I, Cameron-Traub E, Miners JO, Lelo A, Birkett DJ (1988) Biochemical validation of self-reported caffeine consumption during caffeine fading. J Behav Med 11:15–30
- James JE, Gregg ME, Kane M, Harte F (2005) Dietary caffeine, performance and mood: enhancing and restorative effects after controlling for withdrawal relief. Neuropsychobiology 52:1–10
- Juliano LM, Griffiths RR (2004) A critical review of caffeine withdrawal: empirical validation of symptoms and signs, incidence, severity, and associated features. Psychopharmacology 176:1–29
- Lelo A, Miners JO, Robson R, Birkett DJ (1986a) Assessment of caffeine exposure: caffeine content of beverages, caffeine intake, and plasma concentrations of methylxanthines. Clin Pharmacol Ther 39:54–59
- Lelo A, Miners JO, Robson RA, Birkett DJ (1986b) Quantitative assessment of caffeine partial clearances in man. Br J Clin Pharmacol 22:183–186
- Lieberman HR, Wurtman RJ, Emde GG, Roberts C, Coviella ILG (1987) The effects of low doses of caffeine on human performance and mood. Psychopharmacology 92:308–312
- Mitchell SH, de Wit H, Zacny JP (1995) Caffeine withdrawal symptoms and self-administration following caffeine deprivation. Pharmacol Biochem Behav 51:941–945
- Mumford GK, Evans SM, Kaminski BJ, Preston KL, Sannerud DC, Silverman K, Griffiths RR (1994) Discriminative stimulus and subjective effects of theobromine and caffeine in humans. Psychopharmacology 115:1–8
- Pfeifer RW, Notari RE (1988) Predicting caffeine plasma concentrations resulting from consumption of food or beverages: a simple method and its origin. Drug Intel Clin Pharm 22:953–959
- Phillips-Bute BG, Lane JD (1998) Caffeine withdrawal symptoms following brief caffeine deprivation. Physiol Behav 63:35–39
- Reyner LA, Horne JA (2002) Efficacy of a 'functional energy drink' in counteracting driver sleepiness. Physiol Behav 75:331–335
- Richardson NJ, Rogers PJ, Elliman NA, O'Dell RJ (1995) Mood and performance effects of caffeine in relation to acute and chronic caffeine deprivation. Pharmacol Biochem Behav 52: 313–320
- Robelin M, Rogers PJ (1998) Mood and psychomotor performance effects of the first, but not of subsequent, cup-of-coffee equivalent doses of caffeine consumed after overnight caffeine abstinence. Behav Pharmacol 9:611–618
- Robertson D, Wade D, Workman R, Woosley RL, Oates JA (1981) Tolerance to the humoral and hemodynamic effects of caffeine in man. J Clin Invest 67:1111–1117
- Rogers PJ, Dernoncourt C (1998) Regular caffeine consumption: a balance of adverse and beneficial effects for mood and psychomotor performance. Pharmacol Biochem Behav 59:1039–1045
- Rogers PJ, Richardson NJ, Elliman NA (1995) Overnight caffeine abstinence and negative reinforcement of preference for caffeine-containing drinks. Psychopharmacology 120:457–462
- Rogers PJ, Stephens S, Day JEL (1998) Contrasting performance effects of caffeine after overnight and chronic caffeine withdrawal. J Psychopharmacol 12:A13
- Rogers PJ, Martin J, Smith C, Heatherley SV, Smit HJ (2003) Absence of reinforcing, mood and psychomotor performance effects of caffeine in habitual non-consumers of caffeine. Psychopharmacology 167:54–62
- Rogers PJ, Heatherley SV, Hayward RC, Sears HE, Hill J, Kane M (2005) Effects of caffeine and caffeine withdrawal on mood and cognitive performance degraded by sleep restriction. Psychopharmacology 179:742–752
- Silverman K, Griffiths RR (1992) Low-dose caffeine discrimination and self-reported mood effects in normal volunteers. J Exp Anal Behav 57:91–107

- Silverman K, Mumford GK, Griffiths RR (1994) Enhancing caffeine reinforcement by behavioral requirements following drug ingestion. Psychopharmacology 114:424–432
- Smit HJ, Rogers PJ (2000) Effects of low doses of caffeine on cognitive performance, mood and thirst in low and higher caffeine consumers. Psychopharmacology 152:167–173
- Smith AP (1995) Caffeine, caffeine withdrawal and psychomotor performance: a reply to James. Neuropsychobiology 31:200–201
- Smith AP (2002) Effects of caffeine on human behaviour. Food Chem Toxicol 40:1243–1255
- Streufert S, Pogash R, Miller J, Gingrich D, Landis R, Lonardi L, Severs W, Roache JD (1995) Effects of caffeine deprivation on complex human functioning. Psychopharmacology 118:377– 384
- Tinley EM, Yeomans MR, Durlach PJ (2003) Caffeine reinforces flavour preference in caffeine-dependent, but not long-term withdrawn, caffeine consumers. Psychopharmacology 166:416–423

- van Duinen H, Lorist MM, Zijdewind I (2005) The effect of caffeine on cognitive task performance and motor fatigue. Psychopharmacology (in press)
- Warburton DM (1995) Effects of caffeine on cognition and mood without caffeine abstinence. Psychopharmacology 119:66–70
- Warburton DM, Bersellini E, Sweeney E (2001) An evaluation of a caffeinated taurine drink on mood, memory and information processing in healthy volunteers without caffeine abstinence. Psychopharmacology 158:322–328
- Watson JM, Lunt MJ, Morris S, Weiss MJ, Hussey D, Kerr D (2000) Reversal of caffeine withdrawal by ingestion of a soft beverage. Pharmacol Biochem Behav 66:15–18
- Yeomans MR, Spetch H, Rogers PJ (1998) Conditioned flavour preference negatively reinforced by caffeine in human volunteers. Psychopharmacology 137:401–409
- Yeomans MR, Ripley T, Davies LH, Rusted JM, Rogers PJ (2002) Effects of caffeine on performance and mood depend on the level of caffeine abstinence. Psychopharmacology 164:241–249