

REVIEW ARTICLE

Caffeine, sleep and wakefulness: implications of new understanding about withdrawal reversal

Jack E. James* and Michael A. Keane

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

The broad aim of this review is to critically examine the implications of new understanding concerning caffeine withdrawal and withdrawal reversal in the context of research concerned with the effects of caffeine on sleep and wakefulness. A comprehensive search was conducted for relevant experimental studies in the PubMed and PsycINFO databases. Studies were assessed with particular reference to methodological adequacy for controlling against confounding due to caffeine withdrawal and withdrawal reversal. This assessment was used to clarify evidence of effects, highlight areas of ambiguity and derive recommendations for future research. It was found that researchers have generally failed to take account of the fact that habitual use of caffeine, even at moderate levels, leads to physical dependence evidenced by physiological, behavioural and subjective withdrawal effects during periods of abstinence. Consequently, there has been near-complete absence of adequate methodological controls against confounding due to reversal of withdrawal effects when caffeine is experimentally administered. The findings of what has been a substantial research effort to elucidate the effects of caffeine on sleep and wakefulness, undertaken over a period spanning decades, are ambiguous. Current shortcomings can be redressed by incorporating suitable controls in new experimental designs. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS—caffeine; caffeine withdrawal; withdrawal reversal; sleep; wakefulness

INTRODUCTION

Caffeine (1,3,7-trimethylxanthine) is the most widely consumed psychoactive substance in history, and its use is accompanied by beliefs about putative psychopharmacological effects (James, 1991, 1997a). In particular, it has long been believed that caffeine can enhance human performance and mood, and also that caffeine affects key indices of sleep and wakefulness. However, in relation to the former set of beliefs, that caffeine significantly enhances performance and mood, these have been shown to be unsustainable (James and Rogers, 2005). The crux of the matter is that a large number of empirical studies, conducted over several decades, contained a fundamental flaw arising from the uncritical adoption of the standard

placebo-controlled drug trial (James, 1994a, 1995). The consequent failure to take adequate account of the processes of caffeine withdrawal and withdrawal reversal has, until recently, been so widespread that the majority of studies of the psychopharmacological effects of caffeine on performance and mood should be regarded as ambiguous (James, 1997a; James and Rogers, 2005).

While withdrawal reversal has until recently been largely ignored by researchers interested in the effects of caffeine on performance and mood, it continues to be ignored in research concerned with the effects of caffeine on sleep. Thus, the broad aim of this review is to examine the implications of new understanding concerning withdrawal and withdrawal reversal in the context of research concerned with the effects of caffeine on sleep and wakefulness. The main specific aims are to (a) clarify evidence of caffeine effects on sleep and wakefulness, (b) highlight areas of ambiguity informed by new understanding of the

* Correspondence to: Professor J. E. James, Department of Psychology, National University of Ireland, Galway, Ireland. Tel: + 353 91 512 016. Fax: + 353 91 521 355. E-mail: j.james@nuigalway.ie

effects of caffeine withdrawal and withdrawal reversal and (c) recommend directions for future research.

MAIN BIOLOGICAL MECHANISM OF ACTION AND PHYSICAL DEPENDENCE

Caffeine exerts a variety of pharmacological actions at diverse sites, both centrally and peripherally, with antagonism of endogenous adenosine generally being regarded as the main mechanism of action at typical levels of human consumption (e.g. Dunwiddie and Masino, 2001). Adenosine is a neuromodulator that acts upon specific receptors distributed throughout the body, especially the central nervous system. Having a similar molecular structure to adenosine, caffeine occupies adenosine receptor sites, with A₁ and A_{2A} receptors appearing to be the primary targets. It is believed that adenosine generally functions to inhibit physiological activity, and that it has a specific role in the regulation of sleep and wakefulness. Additionally, adenosine dilates cerebral and coronary blood vessels, acts as an antidiuretic, induces bronchoconstriction and inhibits acid secretion in the gastrointestinal tract (Biaggioni *et al.*, 1991; Carter *et al.*, 1995; Franchetti *et al.*, 1994; LeBlanc and Soucy, 1994). By blocking adenosine receptors, caffeine has effects broadly opposite to those of adenosine.

Adenosine is also believed to have a role in the development of caffeine withdrawal. Chronic exposure to drugs (i.e. frequent or habitual use) may lead to physical dependence, evidenced by the appearance of behavioural, physiological and subjective withdrawal symptoms provoked by abrupt abstinence (e.g. Juliano and Griffiths, 2004). Habitual use of caffeine is thought to result in an increased number of adenosine receptors and/or enhanced affinity, resulting in hypersensitivity during abstinence (Biaggioni *et al.*, 1991; Paul *et al.*, 1993; Von Borstel and Wurtman, 1982; Von Borstel *et al.*, 1983). In humans, sleepiness, lethargy and headache are common symptoms of caffeine withdrawal (Evans and Griffiths, 1999; Griffiths *et al.*, 1990; Hughes *et al.*, 1991; James, 1998; Lane, 1997; Lane and Phillips-Bute, 1998; Phillips-Bute and Lane, 1998; Silverman *et al.*, 1992; Smith, 1987; Stafford and Yeomans, 2005; Streufert *et al.*, 1995; Van Dusseldorp and Katan, 1990). Cessation of as little as 100 mg (one cup of coffee) per day, and possibly considerably less (e.g. Lieberman *et al.*, 1987; Smit and Rogers, 2000), can produce symptoms. These are generally noticed within about 12–16 h, peak at around 24–48 h, abate within 3–5 days and only infrequently extend for up to a week (Griffiths *et al.*, 1990; Hughes *et al.*, 1992, 1993). Moreover, recent

studies show that impairments in psychomotor performance (not necessarily discernible to the individual) are detectable after as little as 6–8 h since caffeine was last ingested (Heatherley *et al.*, 2005).

CAFFEINE WITHDRAWAL AND WITHDRAWAL REVERSAL

In a typical study of the psychopharmacology of caffeine, behavioural and psychological outcome variables are measured in healthy volunteers before and after double-blind administration of caffeine and placebo. Compared to baseline and placebo, changes have often been reported in post-caffeine outcomes. This has been particularly evident in studies of performance and mood, wherein it has often been concluded that caffeine has enhancing properties. However, a critical appraisal of the typical study design shows that the findings yielded are, at best, ambiguous (James, 1994a, 1995; James and Rogers, 2005).

Paralleling the time-honoured practice of placebo-controlled studies of therapeutic drugs, caffeine is typically withheld for a period prior to testing for effects, with the aim of ensuring all participants are equivalent in systemic drug levels at time of testing. Such efforts to achieve experimental control appear especially relevant to the assessment of caffeine effects, because the drug is used daily by most people. Typically, caffeine is consumed in separate portions throughout the day, with fewer portions consumed later in the day, followed by overnight abstinence (James, 1997a). With the half-life of caffeine in healthy adults being approximately 5 h (Pfeifer and Notari, 1988), overnight abstinence usually leads to complete or near-complete elimination of systemic caffeine by early morning (Lelo *et al.*, 1986a, b). Consequently, when employing the placebo-controlled paradigm, caffeine researchers have frequently made 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 are generally entering the early stages of caffeine withdrawal by the time they are tested in the laboratory (typically, at least 12–14 h since caffeine was last ingested). As mentioned above, habitual use of caffeine produces physical dependence, evidenced by the appearance of readily measurable withdrawal symptoms following periods of abstinence (e.g. Juliano and Griffiths, 2004). Thus, in the present context, the crucial question is, to what extent do effects generally attributed to caffeine

represent genuine *net* effects of the drug or *reversal* of withdrawal effects induced by overnight abstinence. To date, only a minority of caffeine studies has controlled for the effects of withdrawal reversal. These have consistently found the effects of caffeine on performance, and to a lesser extent on mood, widely perceived by consumers and researchers alike to be net psychostimulant effects, to be attributable to reversal of withdrawal effects associated with short periods of abstinence from the drug (e.g. Garrett and Griffiths, 1998; James, 1998; James *et al.*, 2005; Robelin and Rogers, 1998; Rogers *et al.*, 2005; Yeomans *et al.*, 2002; see James and Rogers, 2005 for a review).

CAFFEINE, SLEEP AND WAKEFULNESS

The new understanding about withdrawal reversal described above has shown that long-held beliefs about the effects of caffeine on performance and mood are no longer tenable. The purpose of the present review is to examine the implications of this new understanding for what have been equally strong beliefs about the effects of caffeine on sleep and wakefulness. PubMed and PsycINFO databases were comprehensively searched for experimental studies of the effects of caffeine on sleep and wakefulness. The relevant studies may be characterised as having employed a wide array of measurements of objective indices of sleep, wakefulness and psychomotor performance, as well as behavioural self-reports and self-reported subjective responses (e.g. sleep quality, mood). The present review, however, focuses primarily on results provided by objective measurements of sleep and wakefulness. This emphasis is justified for reasons of clarity and brevity, and because overall conclusions can be safely generalised to all the other main categories of measurements that have been employed.

Even cursory examination shows that the key methodological limitations described above in relation to studies of caffeine and performance also typify the extensive literature on caffeine and sleep. An illustrative example is provided by Shilo *et al.* (2002), who employed a double-blind crossover design with caffeine-consuming healthy volunteers given either decaffeinated or regular coffee during each of two 24-h periods separated by 1 week. The study design was delivered twice, once for the purpose of taking actigraphic measurements and a second time for measuring melatonin levels in urine. Actigraphic measurements indicated that caffeine increased sleep latency, adversely affected all other sleep variables (sleep time, sleep efficiency, number of sleep bouts, movement and

fragmentation index) and decreased melatonin excretion in urine. In keeping with a long tradition of research in this field, the results were interpreted as confirming the widely held belief that coffee/caffeine consumption interferes with sleep and promotes wakefulness. However, these conclusions are undermined when considered in light of the new understanding about caffeine withdrawal and withdrawal reversal.

Specifically, by the time participants in the Shilo *et al.* study retired for the night in the decaffeinated coffee condition they had been without caffeine for 24 h and remained caffeine free for an additional 7 h (approximate) while in bed. This timing coincides with the period of peak caffeine withdrawal effects. Given that sleepiness is a confirmed effect of caffeine withdrawal (e.g. Juliano and Griffiths, 2004), it can be seen that the study design employed by Shilo *et al.* was confounded and that the results are entirely ambiguous. Rather than being seen as having demonstrated disruptive effects on sleep, the study could equally be seen as demonstrating the sleep-inducing effects of caffeine withdrawal in the decaffeinated coffee condition, with these effects being reversed when participants ingested caffeine in the regular coffee condition. Indeed, considering the strength of evidence showing sleepiness to be an effect of caffeine withdrawal (e.g. Jones *et al.*, 2000; Juliano and Griffiths, 2004), the withdrawal reversal hypothesis can justifiably be seen as the more plausible of the alternatives. Still a third possibility is that both of the aforementioned interpretations are partially correct, such that caffeine interferes with sleep *and* caffeine withdrawal induces sleepiness which is reversed when caffeine is re-ingested.

Topographic quantitative EEG

EEG studies have been widely interpreted as confirming caffeine as a psychostimulant (e.g. Etevenon *et al.*, 1986; Hasenfratz and Bättig, 1994). However, there is little cause for confidence in the findings, due to researchers having almost entirely ignored the problems of caffeine withdrawal and withdrawal reversal. The crucial relevance of withdrawal is confirmed by evidence that EEG is affected by caffeine withdrawal, and that those effects are reversed when caffeine is re-ingested (Jones *et al.*, 2000; Reeves *et al.*, 1995). Specifically, Jones *et al.* employed a double-blind crossover design in which 10 healthy moderate caffeine consumers (mean 333 mg per day) were observed during a baseline period while maintaining their normal diet (including their usual

caffeine intake), and during two 1-day periods when they consumed caffeine-free diets. During the caffeine-free periods, they received capsules containing placebo or caffeine in amounts equal to their baseline daily consumption. Compared to the caffeine condition, after 21 h of caffeine withdrawal in the placebo condition, EEG theta power was significantly increased (indicating increased sleepiness). Importantly, the EEG pattern was found to be essentially the same in the baseline and caffeine conditions, indicating reversal of the withdrawal effects observed in the placebo condition. The findings may be far-reaching in that they confirm the potential for confounding due to possible caffeine withdrawal whenever clinical and research investigations are conducted using EEG. In summary, although the Jones *et al.* study does not show the effects of long-term caffeine abstinence, it confirms that caffeine withdrawal has effects on brain activity that are reversed when caffeine is re-ingested.

CAFFEINE, SLEEP LOSS AND PERFORMANCE

A large research effort has been aimed at assessing the potential caffeine may have for allaying sleepiness caused by sleep loss and atypical sleep-wake cycles (e.g. shiftwork), with particular interest being paid to the potential of caffeine to ameliorate performance decrements associated with sleep loss. Findings have generally been interpreted as showing that caffeine promotes wakefulness, and researchers have been quick to recommend use of the drug for that purpose (e.g. Rosenthal *et al.*, 1991; Walsh *et al.*, 1990). Indeed, it has become commonplace for caffeine to be recommended as an antidote for shiftwork-induced sleepiness, especially in jobs where sustained optimal performance is required for reasons of safety (e.g. air pilots, air traffic controllers, nurses, nuclear power plant operators). However, sleepiness is a well-established effect of caffeine withdrawal (Juliano and Griffiths, 2004), and until recently confounding due to caffeine withdrawal and withdrawal reversal has been ignored in studies of the effects of caffeine on sleep and performance. Recent evidence (reviewed below) not only fails to support the use of caffeine as a countermeasure to sleepiness-induced performance decrements, it suggests that habitual caffeine use has the potential to exacerbate sleepiness and thereby increase the risk of accident.

Several studies concerned with caffeine's potential to counter the effects of sleep loss were more concerned with performance than sleep *per se*, and as such did not report direct measurements of sleep

parameters. Nevertheless, that body of research is relevant to present considerations, because it has been common for observed improvements in performance to be taken as evidence of caffeine-induced wakefulness. Researchers have been forthright in claiming prophylactic benefits for caffeine, and have done so in relation to sleep loss encountered in such diverse settings as long-distance driving and military operations.

Caffeine, sleep and driving

In a series of experiments, Reyner and Horne (1997, 2000, 2002; Horne and Reyner, 1996, 2001a) claimed to have shown beneficial effects of caffeine beverages, especially a well-known brand of 'functional energy' drink. However, none of the studies conducted by them controlled for confounding due to caffeine withdrawal and withdrawal reversal. An illustrative example is provided by Reyner and Horne (2002) who administered the drink in question, with and without caffeine, to 12 young adults who experienced 5-h sleep restriction on two nights. In the late afternoon following each night, participants drank the assigned beverage 30 min before being tested for 2 h on a driving simulator. On the day caffeine was ingested, simulated driving performance was reported to have improved, and this was interpreted as showing that the drink is beneficial in promoting wakefulness and reducing sleep-related driving incidents.

However, all participants were moderate consumers (2–4 cups of coffee daily), and all were tested between 1400 and 1700 after having consumed no caffeine, other than that administered by the researchers, since 1800 the day before. As such, participants in the no-caffeine condition were assessed after being caffeine deprived for a minimum of 22 h, well beyond the point in time when withdrawal-induced sleepiness and decrements in performance begin to appear. After ingesting caffeine, increased sleepiness and decreased performance were reversed, as would be expected considering the processes of caffeine withdrawal and withdrawal reversal. Thus, rather than demonstrating net increases in wakefulness and performance due to caffeine ingestion, the Reyner and Horne results, while remaining ambiguous, are entirely consistent with the interpretation that participants experienced reversal of withdrawal effects characteristic of physically dependent moderate caffeine consumers during periods of caffeine withdrawal.

It is noteworthy that Reyner and Horne have been aware of the threat that the process of withdrawal reversal poses for the integrity of their studies. In

defending their approach they have repeatedly asserted that participants would not have experienced 'any caffeine withdrawal effects during the driving session' (Horne and Reyner, 2001a, p. 84) and there is 'no evidence that [moderate caffeine] intake would have led to any caffeine withdrawal effects' (Horne and Reyner, 2001a, p.84). These assertions, however, are entirely unfounded and are directly contradicted by abundant evidence. The accumulated research is essentially definitive in showing that caffeine withdrawal induces sleepiness and decreases aspects of psychomotor performance in the context of the habitual 'moderate' use that typifies most of the population (James, 1997a; Juliano and Griffiths, 2004; James and Rogers, 2005).

In a recent study, Philip *et al.* (2006) took the unusual step of experimentally examining the effects of caffeine on sleepiness and driver performance *in situ* (i.e. during 'real [rather than simulated] driving at night'). Participants, were 'not allowed to sleep' before driving 200 km over 90 min (i.e. average speed of 133 km per hour) during the early-morning hours of 0200 to 0330. The experimental vehicle was equipped with dual controls, and a 'professional driving instructor' remained ready to take control 'if needed' and to take control altogether if 'a participant could no longer drive' (p. 787). The main outcome measure was video-confirmed inappropriate line crossings. 'Extended time awake and sleepiness at the wheel' (p. 789) resulted in a significant increase in line crossings, which were found to be fewer in number following 200 mg caffeine than placebo. Philip *et al.* attributed the results to the net effect of caffeine, but no such conclusion is warranted considering their failure to take account of the processes of caffeine withdrawal and withdrawal reversal.

It should be of concern that in study after study, and in advice intended to influence road safety policy (e.g. Horne and Reyner, 2001b), the evidence cited in support of the use of caffeine drinks while driving is ambiguous at best. The bare facts are that most people consume caffeine daily, that sleepiness is initiated and exacerbated by caffeine withdrawal, and susceptibility to these effects occurs within the timeframe of the several hours that frequently separate beverages as typically consumed. Consequently, the cumulative evidence regarding caffeine withdrawal effects points to possible increased, rather than decreased, risk of accident in situations where safety depends on wakefulness.

Increased risk of withdrawal-induced sleepiness can, in theory, be avoided by maintaining systemic caffeine concentrations at the pharmacological levels

needed to allay or reverse withdrawal effects. In practice, such states of perfect pharmacological equilibrium are likely to be achieved inconsistently, if at all, and only at a cost to health and well-being. Short-term attempts at maintaining such equilibrium are likely to create unwanted side effects such as feelings of agitation and acute anxiety (e.g. James and Rogers, 2005), whereas long-term attempts are likely to contribute to chronic health problems such as elevated blood pressure and increased risk of cardiovascular disease (e.g. James, 1997b, 2004; James and Gregg, 2004a). The only certain way of avoiding caffeine withdrawal-induced sleepiness is not to be a caffeine consumer in the first place. As such, it can be seen that caffeine may have implications for road safety, though not necessarily in its frequently proposed role as a countermeasure to sleepiness. Caffeine could pose a risk to road safety as a drug of habitual use, wherein users may experience intermittent withdrawal-induced sleepiness.

Caffeine use in military operations

The potentially serious consequences of not taking adequate account of confounding due to reversal of caffeine withdrawal effects are possibly most dramatically exemplified in the burgeoning literature concerned with caffeine use under the extreme conditions of military combat. Although the details of the methodologies employed have varied, the central design feature of these studies has generally involved healthy young participants experiencing a period of caffeine abstinence followed by sleep restriction, followed by administration of caffeine (withdrawal reversal) or placebo (continued abstinence). Based on results from outcome variables having high face validity (e.g. marksmanship), it has generally been concluded that caffeine enhances operational capabilities (McLellan *et al.*, 2005a, 2005b; Tikuisis *et al.*, 2004). This conclusion has prompted researchers to develop new methods, deemed more suitable than beverages, for delivering caffeine to personnel during active operations, and chewing gum has emerged as the preferred delivery vehicle (Kamimori *et al.*, 2002; LaJambe *et al.*, 2005; Syed *et al.*, 2005).

One group of researchers, responsible for a series of studies involving defence forces from Canada, New Zealand and the United States (McLellan *et al.*, 2005a, 2005b), has claimed that the success of a military operation could depend on the use of caffeine to induce wakefulness in operational personnel suffering sleep deprivation (McLellan *et al.*, 2005a, p. 43). In

reality, studies conducted to date do not justify such conclusions, because all have involved personnel who were already habitually exposed to caffeine (i.e. physically dependent) and none controlled for caffeine withdrawal or withdrawal reversal. For example, McLellan *et al.* (2005a) measured performance 38–46 h after caffeine was last consumed, at a time when withdrawal effects were likely to have been particularly pronounced. However, no account was taken of withdrawal-induced performance decrements in the placebo group, or of withdrawal reversal effects in the caffeine group. Thus, the study was incapable of showing net effects, of caffeine.

Notwithstanding the ambiguous nature of the defence forces studies, the findings appear to create a dilemma for defence authorities. If caffeine is thought to have net beneficial effects on performance (as claimed by some researchers), it follows that personnel might be encouraged to ingest caffeine more continuously and possibly at higher levels than they would ordinarily. As such, it is easy to imagine levels of exposure being reached that not only exacerbate existing levels of performance impairment during times of abstinence, but which may also be detrimental to well-being. On the other hand, if it is accepted that caffeine does not produce material net benefits for performance, there is the certainty of withdrawal-induced impairment occurring during times of critical operational demand when usual caffeine-consuming routines are disrupted. Caffeine withdrawal effects could be avoided or minimised during such times by, for example, chewing caffeine gum. Alternatively, non-use of caffeine could be encouraged to remove susceptibility to withdrawal-induced impairment. Challenging policy decisions may be required to resolve the dilemma between choosing to use maintenance doses of caffeine to avoid withdrawal-induced impairment or complete caffeine abstinence to avoid susceptibility to withdrawal altogether.

Putative restorative effects of caffeine, naps and bright light

A subset of studies of sleep loss has sought to compare the efficacy of caffeine with other wakefulness-promoting strategies, such as naps (Bonnet and Arand, 1994; Bonnet *et al.*, 1995; Schweitzer *et al.*, 2006) and bright light (Hayashi *et al.*, 2003; Jay *et al.*, 2006; Wright *et al.*, 1997, 2000). Again, researchers have either been unaware of the potentially confounding influence of caffeine withdrawal and withdrawal reversal, or have sought to dismiss these concerns

by recruiting only 'moderate' or 'mild' consumers as participants (e.g. Jay *et al.*, 2006; Wright *et al.*, 1997, 2000). However, as mentioned above, caffeine withdrawal effects have been reliably demonstrated following cessation of as little as 100 mg (one moderate-strength cup of coffee) per day and less (e.g. Evans and Griffiths, 1999; Griffiths *et al.*, 1990; Lieberman *et al.*, 1987; Smit and Rogers, 2000). Consequently, considering the overall evidence, there can be little confidence in the conclusions and recommendations recently promulgated by a Task Force established by the American Academy of Sleep Medicine to examine the use of caffeine (and other stimulants) for countering the effects of sleep loss (Bonnet *et al.*, 2005). The available evidence does not justify the Task Force's claim that caffeine is an effective sleep-loss prophylactic.

CONTROL FOR CONFOUNDING DUE TO CAFFEINE WITHDRAWAL

Although the central problems of caffeine withdrawal and withdrawal reversal have long been inadequately addressed, systematic attempts at control are beginning to emerge. Approaches have varied, but generally fall into three broad categories, consisting of studies that compare consumers and low/non-consumers, pre-treatment and ad lib consumption studies and long-term withdrawal studies. When these various approaches have been adopted in investigations of the effects of caffeine on performance and mood, only the last of the three has proven successful (see James, 1997a; James and Rogers, 2005). Because of the shortcomings of the first two approaches (studies comparing consumers with low/non-consumers and pre-treatment/ad lib consumption studies) have been considered elsewhere (James, 1997a; James and Rogers, 2005), only the third approach (long-term withdrawal) is considered here.

Studies by James (e.g. James, 1994b, 1994c, 1998) provide an illustration of the use of 'long-term' withdrawal to elucidate net caffeine effects. Taking the core features of the traditional drug-challenge paradigm, with its attendant strengths of double blinding and placebo control, that paradigm has been extended to include four consecutive 1-week periods, with a strictly prescribed and biologically verified regimen of caffeine intake for every day of each week (Table 1). During caffeine phases, participants ingest the approximate equivalent of 1 cup of coffee three times daily, thereby simulating the typical population pattern of caffeine consumption. The protocol employs six consecutive days of placebo/caffeine

Table 1. Summary of a double-blind placebo-controlled crossover protocol incorporating alternating periods of 'long-term' caffeine exposure and abstinence^a

Week	Run-in days (Days 1–6)	'Challenge' (Day 7)	Condition (abbrev.)	Effects revealed by challenge
1	Placebo	Placebo	PP	Sustained abstinence (i.e. caffeine 'wash out'). Serves as a caffeine-free baseline
2	Placebo	Caffeine	PC	Acute challenge. When compared to PP and CC, reveals the presence of tolerance
3	Caffeine	Placebo	CP	Acute abstinence. When compared to PP and CC, reveals the presence of withdrawal
4	Caffeine	Caffeine	CC	Habitual use. When compared to PP, reveals the net effects of habitual consumption

PP, Placebo ingested for 6 consecutive days followed by 1 day of placebo challenge; PC, 6 days of placebo followed by 1 day of caffeine challenge; CP, 6 days of caffeine followed by 1 day of placebo challenge; CC, 6 days of caffeine followed by 1 day of caffeine challenge. ^aDesign originally described by James (1994a, 1994b, 1998), versions of which have been employed in subsequent studies (James and Gregg, 2004a, 2004b; James *et al.*, 2005).

intake to achieve stability of responding before 'challenging' participants on the 7th day of each alternating 1-week period. The 1-week timeframe was chosen on the grounds that complete tolerance has not been confirmed in human studies, and in the few reports of partial tolerance (e.g. in relation to blood pressure) effects have been found to plateau within 3–5 days of continuous use (Denaro *et al.*, 1991; James, 1994b; Robertson *et al.*, 1981). In addition, withdrawal effects (as noted above) have generally been found to abate within a similar timeframe of 3–5 days (e.g. Griffiths *et al.*, 1986; Hughes *et al.*, 1993). The inclusion of alternating periods of caffeine exposure and abstinence offers the substantial benefit of being able to examine and compare the separate acute and chronic effects of caffeine in the one experiment.

Long-term caffeine withdrawal studies have provided strong support for the withdrawal reversal hypothesis in relation to performance and mood, and to a lesser extent, in relation to sleep and wakefulness (James and Rogers, 2005). Overnight caffeine abstinence has been found to be detrimental to performance and mood, with these adverse effects being removed when caffeine is re-ingested (restoration due to reversal of withdrawal effects). Importantly, recent studies yielded no evidence of caffeine having net beneficial effects on performance or mood under conditions of sustained caffeine use versus sustained abstinence (James, 1998; James and Gregg, 2004b; James *et al.*, 2005). Other studies performing similar comparisons have reported similar results in relation to performance and mood in adults (Garrett and Griffiths, 1998; Judelson *et al.*, 2005; Richardson *et al.*, 1995; Rogers and Dernoncourt, 1998; Rogers *et al.*, 2005), children (Heatherley *et al.*, 2006) and in relation to caffeine reinforcement (Garrett and Griffiths, 1998; Tinley *et al.*, 2003).

Although studies of caffeine withdrawal and withdrawal reversal have been mostly concerned with performance and mood, some have examined these parameters in the context of manipulations of sleep. For example, James *et al.* (2005) examined the effects of dietary caffeine on performance and mood in 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. 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, James and Gregg (2004b) found that caffeine exacerbated the marked adverse effects of sleep restriction on mood. 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 (withdrawal reversal). In contrast, the significantly better levels of performance on the same tasks shown by long-term (3 weeks) withdrawn participants were not improved by caffeine. Additionally, acute caffeine withdrawal had a variety of negative effects on mood.

Overall, the results of recent studies of the effects of caffeine on performance and mood (e.g. James and Gregg, 2004b; James *et al.*, 2005; Judelson *et al.*, 2005; Rogers *et al.*, 2005) highlight the urgent need for similar caffeine research in which sleep and wakefulness are measured directly. By 'similar research' it is meant long-term withdrawal studies that control for caffeine withdrawal and withdrawal reversal. At the same time, on a note of caution in relation to the specific design outlined in Table 1, it

should be acknowledged that no single experimental design is likely to address all possible sources of confounding. Regarding the design in question, care was taken to base the length of the alternating phases of caffeine exposure and abstinence on empirical evidence suggesting 6 days should in general be sufficient to control for the processes of withdrawal, withdrawal reversal and tolerance. In reality, longer periods, possibly as long as several weeks or months, might actually be needed to completely control all confounding influences from such processes. Accordingly, studies incorporating longer exposure and abstinence periods would be welcomed, though the benefits of longer phases would need to be weighed against the increased demand on participants' time and the higher research costs that would be involved.

CONCLUSIONS: THE FUTURE

The main conclusion of this review is that the substantial research effort to elucidate the effects of caffeine on sleep and wakefulness, undertaken over a period spanning decades, has produced relatively few findings that can be interpreted with confidence. At the heart of the problem is the general failure of researchers to recognise that habitual use of caffeine, even at moderate levels, leads to physical dependence evidenced by measurable behavioural and subjective effects in response to abstinence involving periods as short as 6–8 h. Because researchers have generally not controlled for withdrawal and reversal of withdrawal effects, results have been ambiguous and conclusions open to challenge. These shortcomings parallel those that long existed in studies of the effects of caffeine on performance and mood. In more recent studies that have controlled for reversal of withdrawal effects, findings have not supported long-held beliefs about caffeine as a general enhancer of performance and mood. Were similar studies to be conducted in relation to sleep and wakefulness, it remains to be seen what effects would be evident.

James and Rogers (2005, p. 6) have argued that 'future research into the effects of caffeine on performance and mood must include effective experimental controls against confounding due to reversal of withdrawal effects'. An equally pressing need exists in relation to research into the effects of caffeine on sleep and wakefulness. The few adequately controlled studies that exist have been mostly concerned with the adverse effects of sleep loss on performance and mood, and the potential of caffeine to counteract such effects. These studies suggest that caffeine actually exacerbates, rather than benefits,

performance and mood degraded by sleep loss. More studies are needed, especially in relation to the implications of caffeine as a countermeasure to sleepiness in a host of important real-life settings, such as long-distance driving, shift work and military operations, in which caffeine has been claimed by some to offer substantial, even life-saving, benefits. However, rather than decrease risk of harm, there is potential for dietary caffeine to increase risk of mishap arising from sleepiness being exacerbated when consumers experience periods of relative caffeine deprivation. Thus, a similar conclusion to that which has been drawn in relation to the effects of caffeine on performance and mood is warranted in relation to research into the effects of caffeine on sleep and wakefulness; namely, future studies must include long-term withdrawal to control against confounding due to reversal of withdrawal effects.

REFERENCES

- Biaggioli I, Paul S, Puckett A, Arzubiaga C. 1991. Caffeine and theophylline as adenosine receptor antagonists in humans. *J Pharmacol Exp Ther* **258**: 588–593.
- Bonnet MH, Arand DL. 1994. Impact of naps and caffeine on extended nocturnal performance. *Physiol Behav* **56**: 103–109.
- Bonnet MH, Gomez S, Wirth O, Arand D. 1995. The use of caffeine versus prophylactic naps in sustained performance. *Sleep* **18**: 97–104.
- Bonnet MH, Balkin TJ, Dinges DF, Roehrs T, Rogers NL, Wesensten NJ. 2005. The use of stimulants to modify performance during sleep loss: a review by the sleep deprivation and stimulant task force of the American Academy of Sleep Medicine. *Sleep* **28**: 1163–1187.
- Carter AJ, O'Connor WT, Carter MJ, Ungerstedt U. 1995. Caffeine enhances acetylcholine release in the hippocampus *in vivo* by a selective interaction with adenosine A1 receptors. *J Pharmacol Exp Ther* **273**: 637–642.
- Denaro CP, Brown CR, Jacob PI, Benowitz NL. 1991. Effects of caffeine with repeated dosing. *Eur J Clin Pharmacol* **40**: 273–278.
- Dunwiddie TV, Masino SA. 2001. The role and regulation of adenosine on the central nervous system. *Annu Rev Neurosci* **24**: 31–55.
- Etevenon P, Peron-Magnan P, Guillou S, *et al.* 1986. Caffeine and EEG mapping: effects of visuo-spatial task in healthy volunteers. *Neurophysiol Clin* **18**: 355–367.
- Evans SM, Griffiths RR. 1999. Caffeine withdrawal: a parametric analysis of caffeine dosing conditions. *J Pharmacol Exp Ther* **289**: 285–294.
- Franchetti P, Messini L, Cappellacci L, *et al.* 1994. 8-Azaxanthine derivatives as antagonists of adenosine receptors. *J Med Chem* **37**: 2970–2975.
- Garrett BE, Griffiths RR. 1998. Physical dependence increases the relative reinforcing effects of caffeine versus placebo. *Psychopharmacology* **139**: 195–202.
- 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, Evans SM, Heishman SJ, *et al.* 1990. Low-dose caffeine physical dependence in humans. *J Pharmacol Exp Ther* **255**: 1123–1132.
- Hasenfratz M, Bättig K. 1994. Acute dose-effect relationships of caffeine and mental performance, EEG, cardiovascular and subjective parameters. *Psychopharmacology* **114**: 281–287.
- Hayashi M, Masuda A, Hori T. 2003. The alerting effects of caffeine, bright light and face washing after a short daytime nap. *Clin Neurophysiol* **114**: 2268–2278.
- Heatherley SV, Hayward RC, Seers HE, Rogers PJ. 2005. Cognitive and psychomotor performance, mood, and pressor effects of caffeine after 4,6 and 8 h caffeine abstinence. *Psychopharmacology* **178**: 461–470.
- Heatherley SV, Hancock KMF, Rogers PJ. 2006. Psychostimulant and other effects of caffeine in 9- to 11-year-old children. *J Child Psychol Psychiatr* **47**: 135–142.
- Horne JA, Reyner LA. 1996. Counteracting driver sleepiness: effects of napping, caffeine and placebo. *Psychophysiology* **33**: 306–309.
- Horne JA, Reyner LA. 2001a. Beneficial effects of an “energy drink” given to sleepy drivers. *Amino Acids* **20**: 83–89.
- Horne JA, Reyner LA. 2001b. Sleep-related vehicle accidents: some guidelines for road safety policies. *Transportation Research Part F: Traffic Psychology and Behaviour* **4**: 63–74.
- Hughes JR, Higgins ST, Bickel WK, *et al.* 1991. Caffeine self-administration, withdrawal, and adverse effects among coffee drinkers. *Arch Gen Psychiatry* **48**: 611–617.
- Hughes JR, Oliveto AH, Helzer JE, Higgins ST, Bickel WK. 1992. Should caffeine abuse, dependence, or withdrawal be added to DSM-IV and ICD-10? *Am J Psychiatry* **149**: 33–40.
- 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. 1991. *Caffeine and Health*. Academic Press: London.
- James JE. 1994a. Does caffeine enhance or merely restore degraded psychomotor performance? *Neuropsychobiology* **30**: 124–125.
- James JE. 1994b. Chronic effects of habitual caffeine consumption on laboratory and ambulatory blood pressure levels. *J Cardiovasc Risk* **1**: 159–164.
- James JE. 1994c. 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. 1997a. *Understanding Caffeine: A Biobehavioural Analysis*. Sage Publications: Thousand Oaks, CA.
- James JE. 1997b. Caffeine and blood pressure: habitual use is a preventable cardiovascular risk factor. *Lancet* **349**: 279–281.
- James JE. 1998. Acute and chronic effects of caffeine on performance, mood, headache, and sleep. *Neuropsychobiology* **38**: 32–41.
- James JE. 2004. A critical review of dietary caffeine and blood pressure: a relationship that should be taken more seriously. *Psychosom Med* **66**: 63–71.
- James JE, Gregg ME. 2004a. Hemodynamic effects of dietary caffeine, sleep restriction, and laboratory stress. *Psychophysiology* **41**: 914–923.
- James JE, Gregg ME. 2004b. Effects of dietary caffeine on mood when rested and sleep restricted. *Hum Psychopharmacol Clin Exp* **19**: 333–341.
- James JE, Rogers PJ. 2005. Effects of caffeine on performance and mood: withdrawal reversal is the most plausible explanation. *Psychopharmacology* **182**: 1–8.
- 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.
- Jay SM, Petrilli RM, Ferguson SA, Dawson D, Lamond N. 2006. The suitability of a caffeinated energy drink for night-shift workers. *Physiol Behav* **87**: 925–931.
- Jones HE, Herning RI, Cadet JL, Griffiths RR. 2000. Caffeine withdrawal increases cerebral blood flow and alters quantitative electroencephalography (EEG) activity. *Psychopharmacology* **147**: 371–377.
- Judelson DA, Armstrong LE, Sokmen B, Roti MW, Casa DJ, Kellogg MD. 2005. Effect of chronic caffeine intake on choice reaction time, mood, and visual vigilance. *Physiol Behav* **85**: 629–634.
- 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.
- Kamimori GH, Karyekar CS, Otterstetter R, *et al.* 2002. The rate of absorption and relative bioavailability of caffeine administered in chewing gum versus capsules to normal healthy volunteers. *Int J Pharm* **234**: 159–167.
- LaJambe CM, Kamimori GH, Belenky G, Balkin TJ. 2005. Caffeine effects of recovery sleep following 27 h total sleep deprivation. *Aviat Space Environ Med* **76**: 108–113.
- Lane JD. 1997. Effects of brief caffeinated-beverage deprivation on mood, symptoms and psychomotor performance. *Pharmacol Biochem Behav* **58**: 203–208.
- Lane JD, Phillips-Bute BG. 1998. Caffeine deprivation affects vigilance performance and mood. *Physiol Behav* **65**: 171–175.
- LeBlanc J, Soucy J. 1994. Hormonal dose-response to an adenosine receptor agonist. *Can J Physiol Pharmacol* **72**: 113–116.
- Lelo AJ, Miners JO, Robson RA, 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 AJ, 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.
- McLellan TM, Kamimori GH, Bell DG, Smith IG, Johnson D, Belenky G. 2005a. Caffeine maintains vigilance and marksmanship in simulated urban operations with sleep deprivation. *Aviat Space Environ Med* **76**: 39–45.
- McLellan TM, Kamimori GH, Voss DM, Bell DG, Cole KG, Johnson D. 2005b. Caffeine maintains vigilance and improves run times during night operations for special forces. *Aviat Space Environ Med* **76**: 647–654.
- Paul S, Kurunwune B, Biaggioni I. 1993. Caffeine withdrawal: apparent heterologous sensitization to adenosine and prostacyclin actions in human platelets. *J Pharmacol Exp Ther* **267**: 838–842.
- Pfeifer RW, Notari RE. 1988. Predicting caffeine plasma concentrations resulting from consumption of food or beverages: a simple method and its origin. *Drug Intell Clin Pharm* **22**: 953–959.
- Philip P, Taillard J, Moore N, *et al.* 2006. The effects of coffee and napping on nighttime highway driving. *Ann Intern Med* **144**: 785–791.
- Phillips-Bute BG, Lane JD. 1998. Caffeine withdrawal symptoms following brief caffeine withdrawal. *Physiol Behav* **63**: 35–39.
- Reeves RR, Struve FA, Patrick G, Bullen JA. 1995. Topographic quantitative EEG measures of alpha and theta power changes during caffeine withdrawal: preliminary findings from normal subjects. *Clin Electroencephalogr* **26**: 154–162.

- Reyner LA, Horne JA. 1997. Suppression of sleepiness in drivers: combination of caffeine with a short nap. *Psychophysiology* **34**: 721–725.
- Reyner LA, Horne JA. 2000. Early morning driver sleepiness: effectiveness of 200 mg caffeine. *Psychophysiology* **37**: 251–256.
- 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, Heatherly SV, Hayward RC, Seers 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.
- Rosenthal L, Roehrs T, Zwyghuizen-Doorenbos A, Plath D, Roth T. 1991. Alerting effects of caffeine after normal and restricted sleep. *Neuropsychopharmacology* **4**: 103–108.
- Schweitzer PK, Randazzo AC, Stone K, Erman M, Walsh JK. 2006. Laboratory and field studies of naps and caffeine as practical countermeasures for sleep-wake problems associated with night work. *Sleep* **29**: 39–50.
- Shilo L, Sabbah H, Hadari R, *et al.* 2002. The effects of coffee consumption on sleep and melatonin secretion. *Sleep Med* **3**: 271–273.
- Silverman K, Evans SM, Strain EC, Griffiths RR. 1992. Withdrawal syndrome after the double-blind cessation of caffeine consumption. *N Engl J Med* **327**(16): 1109–1114.
- 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 R. 1987. Caffeine withdrawal headache. *J Clin Pharm Ther* **12**: 53–57.
- Stafford LD, Yeomans MR. 2005. Caffeine deprivation state modulates coffee consumption but not attentional bias for caffeine-related stimuli. *Behav Pharmacol* **16**: 559–571.
- Streufert S, Pogash R, Miller J, *et al.* 1995. Effects of caffeine deprivation on complex human functioning. *Psychopharmacology* **118**: 377–384.
- Syed SA, Kamimori GH, Kelly W, Eddington ND. 2005. Multiple dose pharmacokinetics of caffeine administered in chewing gum to normal healthy volunteers. *Biopharm Drug Dispos* **26**: 403–409.
- Tikuisis P, Keefe AA, McLellan TM, Kamimori G. 2004. Caffeine restores engagement speed but not shooting precision following 22 h of active wakefulness. *Aviat Space Environ Med* **75**: 771–776.
- 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 Dusseldorp M, Katan B. 1990. Headache caused by caffeine withdrawal among moderate coffee drinkers switched from ordinary to decaffeinated coffee: a 12-week double-blind trial. *Br Med J* **300**: 1558–1559.
- Von Borstel RW, Wurtman RJ. 1982. Caffeine withdrawal enhances sensitivity to physiologic level of adenosine in vivo. *Fed Proc* **41**: 1669.
- Von Borstel RW, Wurtman RJ, Conlay LA. 1983. Chronic caffeine consumption potentiates the hypotensive action of circulating adenosine. *Life Sci* **32**: 1151–1158.
- Walsh JK, Muehlbach MJ, Humm TM, Stokes Dickens Q, Sugerman JL, Schweitzer PK. 1990. Effect of caffeine on physiological sleep tendency and ability to sustain wakefulness at night. *Psychopharmacology* **101**: 271–273.
- Wright KP, Badia P, Myers BL, Plenzler SC. 1997. Combination of bright light and caffeine as a countermeasure for impaired alertness and performance during extended sleep deprivation. *J Sleep Res* **6**: 26–35.
- Wright KP, Myers BL, Plenzler SC, Drake CL, Badia P. 2000. Acute effects of bright light and caffeine on nighttime melatonin and temperature levels in women taking and not taking oral contraceptives. *Brain Res* **873**: 310–317.
- 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.