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ORIGINAL INVESTIGATION

Effects of caffeine on alertness as measured by infrared reflectance oculography

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Abstract
Rationale Caffeine is a well-known stimulant that can be used to increase alertness and performance especially in low arousal situations such as monotonous highway driving or after sleep deprivation. The effects of caffeine in rested, alert, participants are less clear, and this may be attributable to difficulties in objectively assessing small changes in alertness.
Objectives The present study examined the effects of caffeine in non-sleep-deprived participants with methods that have previously been shown to be sensitive to changes in alertness. In order to avoid confounding results, low, or non-users of caffeine, were sought as participants.
Materials and methods Twelve subjects participated in a within-subjects double-blind placebo-controlled design study and were administered either a capsule containing 200 mg of caffeine or placebo on two separate days. Ten-minute long tests of vigilance were performed at baseline and then at 30, 60, 120, 180, and 240 min after swallowing the capsule. During vigilance tests, eye blink variables were measured using infrared reflectance oculography and converted into a drowsiness score, Johns Drowsiness Scale (JDS).
Results Caffeine significantly reduced JDS scores (drowsiness) and reaction times, and these changes persisted for 3 to 4 h. Self reports of sleepiness were not as sensitive, with Karolinska Sleepiness Scale scores only being significantly lower in the caffeine compared to placebo condition at 30 min post capsule administration.
Conclusions The results demonstrated that despite being well rested, administration of caffeine significantly increased alertness and enhanced performance, and these changes were able to be detected with the JDS.

Keywords Alertness · Blinks · Caffeine · Vigilance · Drowsiness scale · Infrared reflectance

Caffeine is one of the most commonly used of all psychotropic drugs in today's society (Fredholm et al. 1999). When administered to sleep-deprived participants, it has been shown to increase performance and arousal level. Specifically, caffeine has been found to decrease reaction times, increase sleep latency, and decrease physiological signs of sleepiness in the electroencephalogram (Beaumont et al. 2001; Patat et al. 2000; Wesensten et al. 2005). Performance in alert subjects often improves with the administration of caffeine, but the magnitude is usually smaller than in participants with lowered arousal levels (Lorist et al. 1994; Smith et al. 2005; Vanderveen et al. 2001).

Difficulties in objectively measuring drowsiness also make it problematic to assess caffeine's effects on alertness in alert (non-sleep-deprived) people. The effects have previously been studied with physiological recordings, measures of performance (e.g., reaction times), and self ratings. A new system to measure alertness/drowsiness has become available and has not yet been studied in

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combination with caffeine (Optalert™, Johns et al. 2006). This system utilizes infrared reflectance oculography to measure ocular variables, which are incorporated into a drowsiness score, the Johns Drowsiness Scale (JDS; Johns et al. 2007). The JDS has been shown to indicate decreases in alertness associated with sleep deprivation and correlates significantly with reaction times, lapses in performance, and lane departures in a driving simulator (Johns et al. 2007; Johns et al. 2006).

To the authors' knowledge, no studies have examined the effects of caffeine on blink duration or velocity or the effects of caffeine on any ocular variable in alert participants. A limited number of studies have examined the effects of caffeine on ocular variables in sleep-restricted or sleep-deprived participants, but generally, these studies fail to show any effect. Previously, caffeine has not effected pupil diameter, pupil contraction latency (Minzhong et al. 2004), or blink rate (Horne and Reyner 1996) and only indicated trends towards increased saccade velocities (Minzhong et al. 2004). The only other study that could be found regarding caffeine and ocular variables was one where clonidine was administered in order to lower arousal levels (Smith et al. 2003). Interestingly, the caffeine was able to counteract the decreases shown in saccade velocity caused by clonidine (Smith et al. 2003). It is possible that in these previous studies, the ocular variables measured were not sensitive enough to changes in alertness generally in order to demonstrate changes in alertness due to caffeine consumption. For example, variables such as blink rate and saccade velocity have been shown to correlate poorly with decrements in performance when sleep-deprived (Bocca and Denise 2006; Caffier et al. 2003).

The aim of the present study was to assess any differences in a newly developed drowsiness score based on ocular variables (JDS) after the administration of caffeine in non-sleep-deprived individuals. As the JDS has been shown to be sensitive to changes in drowsiness/alertness due to sleep deprivation, it was expected to be effected by caffeine. Reaction times from a vigilance test and self reports of sleepiness were measured to support the validity of any changes observed in the oculography based JDS. These measures were also expected to be effected by caffeine and to change in a similar manor to the JDS scores.

Materials and methods

Twelve participants (M/F=5/7) with a mean age of 22 years (SD=4.0, range 18–29 years) were involved in the experiment. The study was approved by the Swinburne University Human Research Ethics Committee, and all participants provided written informed consent. They attended two experimental days, which were separated by a minimum of 3 days. Participants were asked to aim for between 7 and 8 h of sleep the night proceeding each experimental day and to refrain from consuming any form of caffeine from midnight prior to an experimental day, until the end of testing.

Participants were asked a series of questions related to their habitual caffeine use. This included whether they regularly consumed caffeine, and if yes, on average how many caffeinated products they consumed per day. They were also asked to specify the type and number of each caffeinated product. Using standard values of caffeine content of products, an estimate of caffeine consumption within the participant sample was calculated. Coffee, tea, and energy drinks were considered to contain 100, 40, and 80 mg, respectively (Food Standards Australia New Zealand 2006). On each experimental day, participants also indicated the last time that they had consumed caffeine and specified what type of caffeinated product it was.

All participants had normal vision requiring no correction and were not taking any medication that could directly influence alertness. Two female participants did report use of oral contraceptives, and one smoked on a regular basis, which could have interacted with the caffeine administered during the study (Abernethy and Todd 1985; Parsons and Neims 1978). Participants reported to be free of any sleep disorders, and their Epworth Sleepiness Scale scores indicated normal levels of daytime sleepiness (mean=6.6, SD=3.3; Johns 1991).

Each experimental day involved six testing sessions, during each of which participants performed a 10-min version of the Johns Test of Vigilance (JTV; Johns et al. 2007). This simple reaction time task involves a push button response to a brief change in shape of three circles presented on a computer screen that occurred at random intervals of between 5 and 15 s. There were between 50 and 64 such stimuli presented per session. To ensure equal samples per participant and session, only the last 50 reaction times in each session for each participant were analyzed.

Test sessions were scheduled at baseline (approximately 9 am) and then at 30, 60, 120, 180, and 240 min after administration of either 200 mg of caffeine or a placebo. Participants and experimenter were blind to which capsule was being administered. The order of administration was counterbalanced, with half the participants taking caffeine on their first experimental day and the other taking the placebo. Once participants began the experimental day they were allowed to eat only apples and dry biscuits and to drink only water. They passed the time between testing sessions by reading and doing other quiet activities.

Whilst participants performed the JTV, their eye and eyelid movements were monitored by infrared reflectance oculography (Optalert™; Johns et al. 2006). This system

measures the relative velocity of the eyelids opening and closing and the total duration of blinks through infrared transducers positioned towards the eye. Previous studies have determined these to be important variables, which change from when a participant is alert and performing well to when they are drowsy and suffering performance decrement (Johns 2003; Johns et al. 2007). These variables are combined to produce a drowsiness score from 0 to 10 (JDS) each minute. The JDS is based on a weighted combination of the aforementioned ocular variables and is also sensitive to drowsiness (Johns et al. 2007; Johns et al. 2006). In the present study, the Optalert™ system calculated JDS values automatically; however, description of the method used to determine JDS scores is available in Johns et al. (2007). As this system is self calibrating, it can take about 4 or 5 min at the beginning to produce JDS scores. In this study, the minimum number of JDS scores was four in any one 10-min session. Only the last four JDS values per session were analyzed to ensure equal samples per person and session. Participants also rated their sleepiness after each JTV on the modified Karolinska Sleepiness Scale (KSS; Akerstedt and Gilberg 1990).

An analysis of variance (ANOVA) was performed separately for reaction times, JDS and KSS scores, with the main effects being drug (caffeine vs placebo), time (time after taking capsule), order (first vs second experimental day), and participants. Post hoc dependent *t* tests were performed for significant main effects for drug at each testing session.

Results

Only six of the 12 participants rated themselves as regular users of caffeine. The average daily caffeine intake across all participants was 66 mg per day (SD=72 mg).

Participants reported no caffeine consumption in the specified time periods. Participants reported sleeping for 7.5 h (SD=0.7 h) the night preceding an experimental day, with no differences in sleep duration between caffeine (M=7.3, SD=0.6) and placebo days [M=7.6, SD=0.8; $F(1, 10)=2.07$, $p=0.18$]. No differences in sleep duration occurred with the order participants performed each session [$F(1, 10)=1.07$, $p=0.33$].

ANOVA revealed significant main effects on JDS scores of drug [$F(1, 557)=26.00$, $p=0.00$], time [$F(5, 557)=3.00$, $p=0.01$], and subject [$F(11, 557)=22.88$, $p=0.00$]. Post hoc dependent *t* tests showed that JDS scores were not significantly different at the baseline sessions ($p=0.27$) between the two drug conditions. JDS was significantly lower at 30, 60, and 120 min after taking caffeine compared to placebo ($p=0.00$, 0.01, and 0.00 respectively). These differences were no longer significant at 180 and 240 min ($p=0.07$ and 0.15; see Fig. 1). The order effect was not significant [$F(1, 557)=0.03$, $p=0.87$].

Reaction times were significantly effected by drug [$F(1, 7181)=138.6$, $p=0.00$], subject [$F(11, 7181)=83.6$, $p=0.00$], and order [$F(1, 7181)=5.3$, $p=0.02$]. Post hoc dependent *t* tests showed that reaction times were not significantly different between the drug conditions at the baseline session ($p=0.73$). Reaction times were significantly shorter after caffeine than after placebo at all other testing times ($p=0.00$; see Fig. 2). The time effect was not significant [$F(5, 7181)=1.1$, $p=0.34$].

KSS scores were found to differ significantly between participants [$F(11, 125)=16.4$, $p=0.00$] and between drug conditions [$F(1, 125)=12.1$, $p=0.00$]. Post hoc dependent *t* tests showed significantly lower sleepiness 30 min after taking caffeine compared with placebo ($p=0.00$) but not at any other testing times ($p>0.05$; see Fig. 3).

Discussion

Overall, the results indicate that despite the participants being rested, their alertness was increased and their performance enhanced by the administration of caffeine. As expected, the JDS scores were significantly reduced when the participants had consumed caffeine compared with a placebo. This effect was evident at 30 min and persisted for almost 3 h, which is consistent with the known pharmacokinetics of caffeine (Arnaud 1987; Liguori et al. 1997; Van Deventer et al. 1992).

Also as expected, the changes in JDS were similar to the changes observed in reaction times. Reaction times were significantly shorter after caffeine administration compared with placebo at each of the time intervals. Interestingly, reaction times remained rather stable from 60 min onwards in the caffeine condition and did not show any evidence of increasing towards the latter sessions, as would be expected

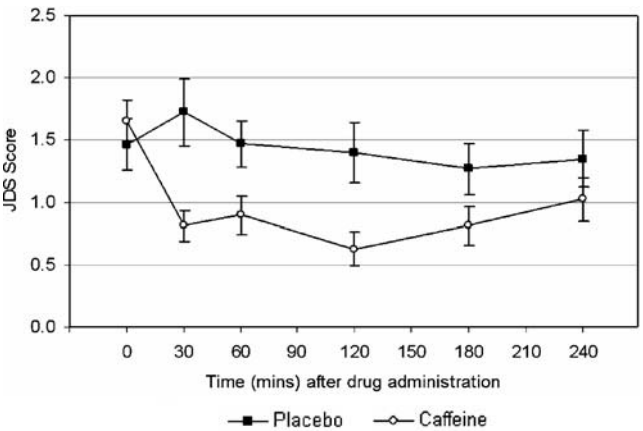

Fig. 1 Mean JDS scores after drug administration. All *bars* represent SEM

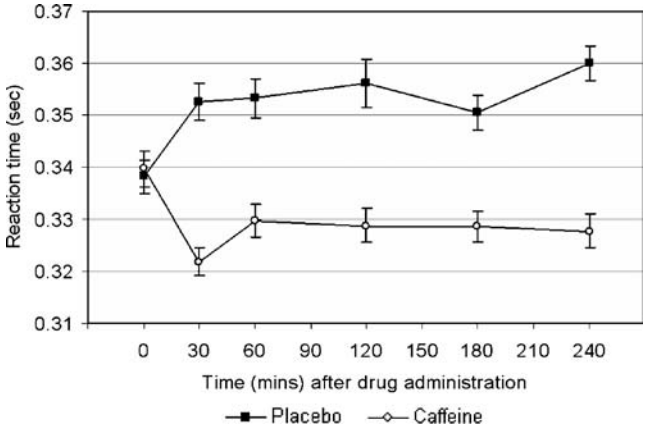

Fig. 2 Mean reaction times after drug administration. All *bars* represent SEM

if the reaction times paralleled the pharmacokinetic properties of caffeine (Arnaud 1987).

The self-reported levels of sleepiness measured with the KSS were not as sensitive to caffeine as the other variables. Self-rated sleepiness only showed significant differences between drug conditions 30 min after capsule administration. This may have been due to the ability of the KSS to detect small changes in arousal in relatively alert participants and may be even due to the significant variability between participants.

The current behavioral results are in line with those found in the sleep-deprived state, which have shown vigilance and reaction times to improve after the administration of caffeine, when compared to placebo (Bonnet et al. 2005; Patat et al. 2000; Wesensten et al. 2005). The reaction time results here are also comparable with studies of alert people showing improvements after caffeine administration (Lorist et al. 1994; Smith et al. 2003; and summarized in Vanderveen et al. 2001).

Previous research regarding the effects of caffeine on ocular variables is limited and generally finds no effect. In the current study, the JDS, which is based on a combination of variables including total blink duration and the velocity of eyelids opening and closing, changed with caffeine administration. No other studies examining these ocular variables are available; however, the current results are in line with trends towards, and significant increases, in saccade velocity with caffeine administration that have been reported by others (Minzhong et al. 2004; Smith et al. 2003).

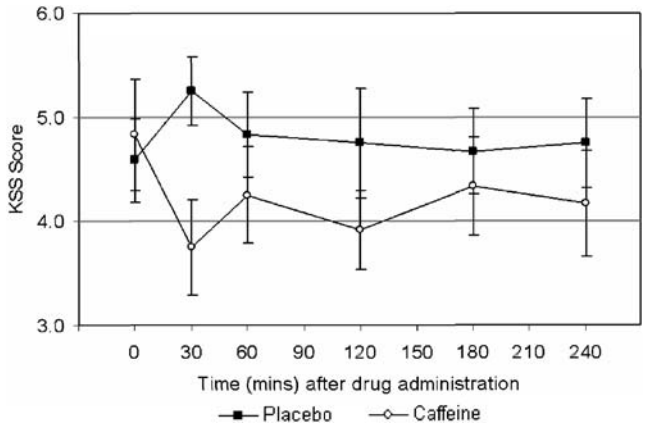

Fig. 3 Mean KSS scores after drug administration. All *bars* represent SEM

The changes in JDS in the current study, however, are in contrast to most other previous research into ocular variables, which have demonstrated no difference in pupil diameter, pupil contraction latency, and blink rate with caffeine administration after sleep restriction or deprivation (Horne and Reyner 1996; Minzhong et al. 2004). One possible explanation as to why others have not observed changes in ocular variables after caffeine administration may be due to the sensitivity of the measures they used to detect changes in alertness generally. Ocular variables such as blink rate and saccade velocity have not proven very effective in detecting changes in alertness/drowsiness caused by sleep deprivation (Bocca and Denise 2006; Caffier et al. 2003), and blink rate has also been shown to be largely effected by individual differences and task (Caffier et al. 2003; Stern et al. 1984), so it is not surprising that they have demonstrated limited or no changes after caffeine administration. The Optalert™ system and JDS do not use such variables. A possible additional advantage of the JDS for detecting changes in alertness due to caffeine administration may be attributed to the use of several ocular variables rather than just one.

Many researchers have indicated the importance of not just relying on one ocular variable to measure drowsiness (Heitmann et al. 2001; Morris and Miller 1996; Van Orden et al. 2000). It may be this combination of variables used to generate the JDS that gives the measure more sensitivity to smaller changes in alertness than would individual measures such as blink rate or pupillary response. This study shows that even when people are reporting hours of sleep at night that are considered to be adequate, their alertness levels during the day can still be improved by caffeine. It is commonly believed that the only known direct effect of caffeine is on adenosine receptors (Fredholm 1995; Fredholm et al. 1999); however, it is possible that the indirect effects of caffeine also contributed to the effects seen here on reaction times and JDS scores.

The current study involved participants that usually ingested only small amounts of caffeine, if any. Thus, the differences in performance, JDS, and KSS seen between caffeine and placebo in this study are accredited to the effects of caffeine on the CNS rather than reversal of caffeine withdrawal suggested to occur in habitual caffeine users (James and Rogers 2005). As a consequence of using low or non-users of caffeine, the dose given to participants

was much higher than they would usually have in daily life. For the purpose of the current study, this dose illustrated the predicted relationships; however, the effects on JDS in particular may be different with a smaller amount of caffeine or in those that have developed a tolerance to caffeine due to regular caffeine consumption. The effects of multiple doses of caffeine may also differ. These points could be a focus of future research. Additionally, the current study only recorded sleep length for the night prior to each experimental day. Thus, it is possible that participants had not been obtaining adequate sleep previous nights and had some level of sleep debt. This could have resulted in participants having some residual adenosine that had not been eliminated with sufficient sleep and must be considered when interpreting results.

In conclusion, the present study gives insight into the effects of caffeine on JDS scores, a measure of alertness/drowsiness based on ocular variables, in alert individuals, most of whom consumed either no caffeine or very little caffeine on a regular basis. The study demonstrated that a moderate dose of caffeine in such individuals can reduce JDS scores, which are a measure of drowsiness. Differences in findings between this study and previous research utilizing different ocular variables to measure alertness/drowsiness may be attributed to the use of ocular variables that are less sensitive to changes in alertness/drowsiness by others. Additionally, the failure of others to combine ocular variables into one index may have influenced differences in results. The changes in reaction times caused by caffeine administration in the present study were also similar to those observed in JDS. Self-rated sleepiness (KSS scores) on the other hand did not appear to be very sensitive to these changes in alertness. Overall, the results of this study demonstrated that administration of caffeine can significantly increase alertness and enhance performance in alert and well-rested individuals, and these changes can be detected using oculography.

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Furthermore, this study was performed in compliance with the current laws of Australia.

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