Memory and attention functions in middle-aged and elderly subjects are unaffected by a low, acute dose of caffeine

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Abstract

SCHMITT, J.A.J., E. HOGERVORST, E.F.P.M. VUURMAN, J. JOLLESAND W.J. RIEDEL. Memory and attention functions in middle-aged and elderly subjects are unaffected by a low, acute dose of caffeine. *PHARMACOL BIOCHEM BEHAV*. The cognitive effects of a low dose (100 mg) of caffeine in middle-aged and elderly subjects were investigated according to a double blind cross-over design. Sixteen middle-aged (45-60 years) and fourteen elderly (60-75 years) healthy men and women, who were regular caffeine consumers, received 100 mg caffeine or placebo on two separate days. Cognitive tests were administered 30 minutes later. Caffeine did not affect short-term memory span or speed, or long-term memory retrieval functions, as was assessed with a word learning test, digit span test and memory scanning test. Although caffeine improved performance on card II of the Stroop Colour Word Test, performance on other sub-tests or the Stroop interference measure were unchanged, showing caffeine did not affect focussed attention. Cognitive performance and effects of caffeine did not differ between middle-aged and old subjects. Also, habitual caffeine use did not influence cognitive performance as such, nor did it alter the effects of caffeine in either age-group. The results indicate that caffeine withdrawal does not affect (short-duration) cognitive performance, even in subjects who normally consume relatively large amounts of caffeine. A low dose (100mg) of caffeine appears to be ineffective in inducing cognitive changes in middle-aged and elderly subjects.

Keywords : caffeine, cognition, memory, attention, age, caffeine-withdrawal

Introduction

Despite several decades of extensive experimental research, the precise effects of caffeine on cognitive functioning remain quite elusive. Attempts to relate caffeine actions to specific cognitive domains, such as learning and memory, are hampered by inconsistent and contradicting results (for reviews see Fredholm et al. 1999, Riedel and Jorissen 1998, Rogers and Dernoncourt 1998). While there are some indications that caffeine, under certain conditions, can influence specific functions, for example long-term memory (Riedel et al. 1995), it appears that caffeine's most consistent effect is an increase in arousal (Herz 1999, Kenemans and Lorist 1995, Watters et al. 1997). Thus, caffeine can be considered a non-specific stimulant (Kenemans and Verbaten 1998) that can indirectly improve human cognitive performance by increasing alertness.

Traditionally, the effect of a non-specific stimulant is seen as reducing the amount of cues that are being utilised while performing a certain task (Easterbrook 1959). Thus, caffeine and other stimulant drugs may be expected to increase selectivity of information processing, in other words, induce a 'narrowing' of attention and reduce distractibility to irrelevant stimuli (Anderson et al. 1989, Kenemans and Lorist 1995, Kenemans and Verbaten 1998). Experimental studies with caffeine have provided evidence supporting this notion (Kenemans and Lorist 1995, Kenemans et al. 1999, Lorist et al. 1994, Lorist et al. 1995). This effect of caffeine is particularly interesting with regard to the results of our previous study, in which caffeine improved performance on a word learning task with distraction (Hogervorst et al. 1998). The effect was interpreted in terms of improved selective attentional processing, i.e. caffeine improved the subjects' ability to focus on the (visually presented) target words, and reduced distraction by the auditory distractor words. However, in a conventional word learning task (without distraction) the affected task parameter, i.e. number of words recalled after one presentation trial, can be seen as an indicator of short-term memory span (Lezak 1995). Thus, an increase in short-term memory span may also underlie the effect. Indeed, caffeine has recently been shown to improve performance on a digit span test (Rees et al. 1999).

Another issue in caffeine research, one that was specifically addressed in our previous study, is a possible interaction between age and the effects of caffeine. The cognitive effects of caffeine may be more pronounced in elderly subjects (Jarvis 1993, Rees et al. 1999, Swift and Tiplady 1988, Yu et al. 1991), although age-related differences in the cognitive effects of caffeine were not always apparent (Amendola et al. 1998, Hameleers et al. 2000, Lorist et al. 1995, Rogers and Dernoncourt 1998, Smith et al. 1999). In our previous study (Hogervorst et al. 1998) it was found that 250 mg caffeine diminished speed of short-term memory search in young subjects only, whereas an improvement was seen of short-term memory span in middle-aged subjects. We proposed that differences in habitual caffeine consumption between age-groups may have caused the differential caffeine effects. Specifically, it was suggested that the high caffeine consumption in the middle-aged group may have rendered them particularly vulnerable to caffeine withdrawal effects in the placebo condition, and this may have lead to poor cognitive performance.

The present study was designed to further investigate the above issues. The aim of the present study was threefold. First, we sought to establish whether the previously observed performance increment in the word learning task was due to an increase in short term memory span or was alternatively caused by narrowing of attention. To this end, we measured the effects of caffeine on a similar word learning task *without* distraction, as well as on a specific short-term memory span test (digit span). We also included the Stroop Colour Word Test to specifically assess selective attention. It was hypothesised that caffeine would not affect performance on either memory test, but would improve performance on the Stroop Test. Second, we wanted to investigate whether the observed differences in performance between middle-aged and old subjects were due to differences in habitual caffeine consumption. Therefore, we matched our age-groups to a level of habitual caffeine use that was similar to that of the middle-aged group in the previous study. It was explicitly decided *not* to try to avoid putative withdrawal effects by using only non-caffeine users. Instead, we aimed to induce similar caffeine withdrawal effects in both age-groups, as it was hypothesised that withdrawal effects were (at least partly) responsible for our previous findings. Also, it would be expected that the facilitating effect of caffeine would be similar in magnitude with a lower dose of caffeine (100 mg) since even small doses are effective in relieving withdrawal effects (Mitchell et al. 1995). Finally, in our previous study there was some indication that caffeine may reduce the slope of the memory scanning function in middle-aged and old subjects, but no significant effect could be detected. In the present study the effects of caffeine on this task were re-investigated according to a cross-over design, which may be more sensitive to detect effects. In addition, stimulus quality in the memory scanning task was modulated to specifically investigate the effect of caffeine on the perceptual processes.

Materials and methods

Subjects

Thirty healthy subjects were recruited from a pool of subjects that had responded to newspaper advertisements requesting volunteers for scientific research. The group consisted of 16 middle-aged subjects, aged 46 to 60 years, and 14 old subjects, aged 60 to 74 years (see table 1 for subject characteristics.). Subjects received ¤ 10,- for their participation. All subjects gave a written informed consent prior to participation. The experiment was carried out in accordance with the Declaration of Helsinki on human subjects.

Subjects were pre-selected over the telephone. They reported to feel healthy and not to use any medication or drugs liable to influence cognitive functioning. Subjects with excessive alcohol consumption (≥ 5 drinks a day) were excluded. Groups were matched for sex, intelligence, and habitual caffeine consumption (in mg/day). Intelligence was inferred from LOA (Level of Occupational Ability). The LOA is based on a detailed functional description (Centraal Bureau voor de Statistiek 1985), each subjects' occupation was transformed to a score that ranged from 1 (simple labour requiring no education or low level of skills) to 7 (highly specialised labour at an academic level) (Directoraat-Generaal voor de arbeidsvoorziening 1989). The LOA may be a better estimator of intelligence in older subjects than years of education.

Habitual caffeine intake was calculated on reported weekly consumption of caffeine-containing coffee, tea and soft drinks, in cups (150ml), mugs (175 ml), glasses (150 ml) or cans (330 ml). Habitual use in milligrams of caffeine a day was calculated using the following average caffeine contents in the Netherlands: coffee: 85 mg/ 150 ml, tea: 30 mg/ 150 ml, cola: 20 mg/ 150 ml.

<TABLE 1 NEAR HERE>

Design and procedure

The study was conducted according to a double-blind, cross-over design. Treatment orders (caffeine-placebo, placebo-caffeine) were balanced for each age group over the two test days. One week before the actual experiment, subjects underwent a training session during which they completed the full test battery. Subjects were instructed not to consume beverages containing caffeine or alcohol on evening before and the morning of the test days. Upon the subject's arrival, two capsules containing either placebo or a total of 100 mg caffeine were dissolved in one cup of decaffeinated coffee. Subjects were instructed to finish the drink within a period of five minutes. Cognitive performance was assessed thirty minutes after finishing the drink. The test battery took approximately 25 minutes to complete. Subjects were seated in front of a computer screen and were given standardised instructions by the same experimenter. After one week, subjects returned for secondsession that was identical except for the content of the drink. All testing was done in the morning.

Cognitive Assessments

Two parallel versions of the Word learning Test and Digit Span test were used for the experiment. A third version of the tests was used for each training session. The order of the two experimental versions was balanced over test days. A single version of the Stroop Colour Word Test was used in all assessments.

Digit Span

The Digit Span test is a sub-test of the Wechsler Adult Intelligence Scale (Wechsler 1981) and is used to test working memory storage capacity or memory span (Lezak 1995). A sequence of 3 randomly chosen and unique digits (from 1 to 9) is slowly read aloud to the subject. If this is correctly reproduced, the set size is augmented with one digit. If the subject fails at two consecutive sequences, the memory span is assumed to be the last sequence that was correctly produced.

Word Learning Test

A list of 15 monosyllabic meaningful nouns is presented on a computer screen with a rate of one word per two seconds. Following this presentation, subjects are asked to verbally recall as many of the presented words as possible (Brand and Jolles 1985). This procedure is repeated three times (immediate recall trials). Thirty minutes after the first trial, subjects are asked to recall the previously learned words (delayed recall trail). Dependent variables are the number of correctly recalled words in each trial. Performance on the first immediate recall trial is a measure of storage capacity in working memory (span), the total number of words recalled in the three immediate recall trials is a measure of short term memory and performance on the delayed recall trial is taken as a measure of long term memory.

The Stroop Colour Word Test

The Stroop Colour Word Test is a test of selective attention (Stroop 1935). The test consists of three subtests. First, a card with a hundred colour names must be read as quickly as possible (card I). Secondly, the same number of coloured patches must be named (card II). On card III colour names are printed in incongruously coloured ink. The colour of the ink must be named, without paying attention to the word itself. The outcome parameters of this test are the time needed to complete each card and the interference measure. The latter denotes the percentage of extra time needed to complete card III, relative to the average of card I and II : (time card III / ((time card I + time card II)/2)) * 100%.

Memory Scanning

Subjects are briefly shown a set of unrelated consonants and are told to memorise them. This is called the "memory set" (Sternberg 1969). Then a series of 120 letters is displayed on a computer screen. The subjects' task was to respond tom each letter as rapidly as possible by pressing either a 'YES' or 'NO' button to indicate whether or not each successive letter was one of those from the memory set. Half of the presented letters were part of the memory set. Also, half of the targets and non-targets were degraded by the addition of speckled noise to the letters. The mean of the response time (RT) for correct responses (on targets and non targets) for degraded and non-degraded stimuli separate was taken as a dependent parameter. This task was performed with memory sets consisting of 2 and 4 letters, respectively.

Statistical analysis

The outcome variables were analysed with a repeated measures Analysis of Variance (MANOVA) according to a 2 (Treatment) x 2 (Age-group) x 2 (Treatment order) factorial model to test the effect of Treatment (caffeine 100mg / placebo), the effect of age-group (middle-aged /

old), the effect of Treatment order (caffeine-placebo, placebo-caffeine) and the interaction effects between these factors. Two additional within-factors were added to the analysis of the Memory Scanning task. These were Memory load (2 letter, 4 letters) and Stimulus quality (degraded, non-degraded). Since habitual caffeine intake was not entirely identical in both age groups this variable was included as covariate in the analyses. In order to test the effect of habitual use on the effect of Treatment and the interaction between Age-group and Treatment, individual differences in performance in the caffeine and placebo conditions were calculated. Differences were then analysed using a one-way analysis of co-variance (ANCOVA) with Age-group as main factor and habitual caffeine intake as covariate.

Results

The results of the cognitive assessments are summarised in table 2. None of the analyses revealed significant interactions involving Treatment order. The only main effect of Treatment order was found in the analysis of the memory scanning task, indicating a group difference in performance.

The outcome measures of the Word Learning Test, i.e. number of words in trial 1, total immediate recall and delayed recall, showed no main effects of Age-group or Treatment, or an interaction between Age-group and Treatment. Similarly, Digit Span performance showed no main effects of Age-group or Treatment, and there was no Treatment by Age-group interaction.

Performance on Card I of the Stroop test showed no main effects of Age-group or Treatment, or an Age-group by Treatment interaction. A main effect of Treatment was found for card II ($F_{1, 28}=4.50$, $p<0.05$), but no effect of Age-group or an interaction was found. Caffeine reduced the time needed to complete card II in both age groups. Time to complete card III and the interference measure showed no main effects of Age-group or Treatment or an interaction between Treatment and Age-group . The error rate was very low and was not statistically tested. The mean total number of errors (card I + II +III) was less than one during caffeine and placebo conditions in both age-groups.

Analysis of the memory scanning revealed a main effect of Memory load (F1,28)=79.53, p<0.001), as well as a main effect of Stimulus quality (F1,28)=6.88, p<0.05). As is to be expected, responses slowed as memory load increased, and responses were also slower for degraded stimuli as compared to non-degraded stimuli. There was no interaction between Memory load and Stimulus quality. No main effects of Treatment or Age-group were seen for the memory scanning test, and no significant interactions between factors were found.

Covariance analysis to establish the effect of habitual caffeine intake revealed that habitual caffeine explained a significant amount of variance of the main effect of Age-group on Digit span performance. However, correction for habitual caffeine intake did not alter the results, i.e. the effect of Age-group remained non-significant. Results of other cognitive assessments were unaffected by the inclusion of habitual caffeine intake as covariate in the analyses.

<TABLE 1 NEAR HERE>

Discussion

In the present study, we examined the effects of 100 mg caffeine and placebo on memory functions and selective attention in middle-aged and old subjects. Caffeine was found not to affect short-term memory span or speed, or long-term memory retrieval functions, as was assessed with a word learning test, digit span test and memory scanning test. Caffeine improved performance on card II of the Stroop Colour Word Test, but no caffeine effects were seen on other subtest or on the Stroop interference measure. Cognitive performance and effects of caffeine did not differ between middle-aged and old subjects. Also, habitual caffeine use was found not to influence the cognitive performance as such, nor did it alter the effects of caffeine in either age-group.

In general, cognitive performance was not different in caffeine and placebo conditions. This suggest that no withdrawal effects, as to cognitive functioning, occurred under placebo in our study groups, despite relatively high habitual caffeine intake. Adverse effects following short-term caffeine deprivation are well known, and these consist mostly of headache, drowsiness and reduced mood (Griffiths and Mumford 1995, Rogers and Dernoncourt 1998). However, caffeine withdrawal effects are less consistently found on objective measures of cognitive performance, especially on short duration tasks (Lane 1997, Phillips-Bute and Lane 1998, Rogers and Dernoncourt 1998). Cognitive withdrawal effects appear to be most pronounced in long duration vigilance-like tests (Lane and Phillips-Bute 1998) and perhaps after longer (48 hours) caffeine deprivation periods (Fredholm et al. 1999).

The results suggest that previously observed improvement of memory test performance (Hogervorst et al, 1998) are not due to caffeine withdrawal during placebo. If this were the case, similar withdrawal effects should have occurred in the present study, given the similarities in habitual caffeine consumption in the present and former study groups. It must be noted that, because no baseline measurements are taken, withdrawal effects can only be inferred by comparison of performance under placebo versus caffeine. Mitchell et al. (1995) have shown that doses of caffeine that are low compared to habitual caffeine intake are sufficient to prevent withdrawal symptoms. Therefore, we can assume that if withdrawal effects were present, administration of 100 mg would have effectively removed these effects, resulting in a better performance under caffeine.

The rejection of the withdrawal hypothesis implies that previous findings (Hogervorst et al, 1998) reflected a true age-related difference in cognitive response to caffeine. However, no evidence could be found for such an age by caffeine interaction in the present study. The relatively low dose of caffeine (100 mg) may account for this, particularly since caffeine withdrawal effects were not apparent. Doses of caffeine below 100 mg have been reported to facilitate vigilance performance (Lieberman et al. 1987) as well as attention and memory (Durlach 1998, Smith et al. 1999), and even in the absence of withdrawal effects (Warburton 1995). However, these effects were observed in relatively young subjects (<40 years), whereas older subjects may benefit more from higher doses (Hogervorst et al. 1998). Interestingly, in a study by Rees et al. (1999) 250 mg caffeine was seen to act differently in young (20-25) and old (50-65) subjects on a number of tests. In young subjects tapping and response time on a rapid processing task was improved under caffeine, whereas caffeine elevated digit span and focussed attention (as measured with a digit cancellation test) in the elderly subjects. Important in this respect was that subjects were allowed to consume their normal caffeine intake until 1.5 to 2 hours before the experiment, hereby minimising any possible withdrawal effects. These data are in line with our current and previous findings, suggesting that elderly may benefit from a higher dose of caffeine (250 mg) particularly on span and/or focussed attention tasks, independent of withdrawal effects.

In conclusion, results of this study indicate that caffeine withdrawal does not substantially affect (short-duration) cognitive performance, even in subjects who normally consume relatively large amounts of caffeine. Certainly, lack of cognitive withdrawal effects needs to be confirmed by incorporation of a baseline measure during which performance is tested under normal caffeine intake. Also, it would be interesting to investigate putative withdrawal effects during prolonged cognitive testing, as this would perhaps reflect a more realistic situation. Secondly, the present results suggest that lower doses of caffeine may be less potent in terms of cognitive effects in elderly subjects. It would be interesting to investigate the effects of higher caffeine dosages in elderly subjects, particularly with regard to focussed attention and short-term memory span.

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Table 1 : Subject characteristics (mean and standard deviation in brackets) of Age, Level of Occupational Ability (LOA), Habitual Caffeine consumption in mg / day (incl. tea and cola).

	Middle aged		**Old**	
Age	54.6	(3.7)	67.7	(5.1)
LOA (1- 7)	4.1	(1.8)	4.5	(1.3)
Caffeine (mg /day)	427	(180)	349	(175)
N	16		14	

Table 2: Means (standard deviations) of the outcome variables of the cognitive assessments, broken down by age-group and treatment. Results printed in italic show a main effect of caffeine.

Measure	**MIDDLE-AGED** caffeine		placebo		**OLD** caffeine		placebo	
Word Learning Test								
trial 1 (# words)	6.9	(2.1)	6.6	(2.1)	6.4	(1.7)	6.4	(1.5)
Immediate recall (# words)	28.8	(6.0)	28.1	(5.9)	26.4	(5.7)	26.3	(5.3)
Delayed recall (# words)	9.6	(2.8)	9.2	(2.8)	8.3	(2.8)	8.5	(2.9)
Digit Span (# digits)	5.6	(1.2)	5.5	(0.8)	5.7	(1.4)	5.6	(1.1)
Stroop Colour Word Test								
card I (sec)	43.4	(5.5)	44.8	(6.0)	44.4	(6.7)	44.8	(6.3)
card II (sec)	*54.4*	*(8.8)*	*57.4*	*(9.1)*	*54.9*	*(10.8)*	*55.9*	*(10.4)*
card III (sec)	84.5	(15.3)	87.9	(15.0)	90.4	(23.2)	91.0	(22.0)
Interference (%)	72.4	(18.8)	71.7	(17.5)	81.5	(33.9)	80.4	(31.0)
Memory Scanning								
Memory load 2 letters								
Degraded stimuli RT	567	(64)	585	(64)	620	(150)	587	(62)
Non-degraded stimuli RT	562	(56)	567	(73)	594	(61)	578	(78)
Memory load 4 letters								
Degraded stimuli RT	726	(150)	681	(116)	720	(91)	717	(92)
Non-degraded stimuli RT	721	(191)	655	(100)	669	(95)	663	(90)