WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 4, 1852-1873. Research Article ISSN 2277– 7105

EFFECTS OF REGULAR CAFFEINE CONSUMPTION ON SEMANTIC MEMORY AND CENTRAL EXECUTIVE FUNCTION: A SECONDARY ANALYSIS

Dominic P. Nguyen-Van-Tam, PhD and Andrew P. Smith, PhD*

Centre for Occupational and Health Psychology, School of Psychology, Cardiff University, 63 Park Place, Cardiff CF10 3AS, UK.

Article Received on
14 Jan. 2023,

Revised on 03 Feb. 2023,
Accepted on 24 Feb. 2023

DOI: 10.20959/wjpr20234-27409

***Corresponding Author**
Andrew P. Smith, PhD
Centre for Occupational and Health Psychology, School of Psychology, Cardiff University, 63 Park Place, Cardiff CF10 3AS, UK.

ABSTRACT

Background: Research has examined the acute effects of caffeine on many aspects of memory. Less is known about the effects of the level of caffeine regularly consumed or how this might interact with the acute effects of caffeine, and this was examined using semantic processing and executive function (logical reasoning) tasks. **Methods**: A secondary analysis of data from three recently published studies is reported. There were 177 participants (university students) in the dataset. Chronic caffeine consumption was analysed in two ways. The first split the samples into quartiles. The second method compared those who consumed less than 30mg of caffeine daily with those with higher consumption levels. After baseline testing, separate groups either received caffeine or a placebo. The caffeine dose was 4mg/kg and was carried out double-blind. **Results**: At baseline, there were no significant effects of regular levels of caffeine consumption. The usual positive effects of acute caffeine were observed in both the semantic processing and logical reasoning tasks. No significant interactions existed between regular caffeine intake and caffeine/placebo groups. **Conclusion**: The results show little effect of the regular level of caffeine consumption and no interactions between this and acute challenge conditions. In contrast, acute effects of caffeine were observed for both tasks, confirming previous findings.

KEYWORDS: Caffeine; Habitual caffeine consumption; Memory; Semantic processing; Executive functioning; Logical reasoning.

INTRODUCTION

Previous research[1-20] has investigated the effects of caffeine on a range of memory systems and processes, and in our recent studies[21-25], we have found that only the effects on semantic memory and executive function are reliable and replicable. The findings so far, however, may not be a complete profile of the effects of caffeine on semantic memory and executive function because, as well as immediate, short-term effects, caffeine could potentially have longer-term effects on the systems as a result of regular levels of caffeine consumption. No previous study has addressed the possibility of long-term caffeine effects on semantic memory and executive function, and the present study aimed to redress this balance by looking at both the main effects of long-term caffeine consumption and interactions of long-term consumption with acute ingestion.

Compared to the investigation of the acute effects, the investigation of the cognitive effects of long-term caffeine consumption has received comparatively little attention. However, several strands of evidence suggest that the effects of caffeine on semantic memory and executive function are a possibility. The first of these strands of evidence comes from animal models where it has been shown for some years that long-term administration of caffeine causes both physiological changes (e.g. increasing the density of adenosine receptors[26-27]) and changes in behaviour.[28] In order to elicit these changes, animal studies have generally used experimental manipulation of long-term caffeine consumption and very high doses, far more than the levels consumed by humans, so it is unknown to what extent the results can be generalised.

The second source of evidence that long-term caffeine consumption has the potential to produce cognitive effects comes from human studies, which have produced a limited amount of evidence that regular caffeine consumption has a positive effect on free recall. Four studies have explicitly examined the effects of chronic caffeine consumption on memory, and all have used free recall as the measure of memory performance. Mitchell and Redman[16] compared small numbers of low (< 120mg/day), medium (120 to 300mg/day) and high (> 300mg/day) caffeine users on a recall task and were unable to find any statistically significant differences between groups. Loke (1988)[15] also looked used a free recall task and was again unable to show any main effects of long-term consumption of caffeine though an interaction between chronic and acute ingestion was found with low background consumers (< 387.5mg/week) showing impaired performance after an acute caffeine challenge. Smith et

al.[29] compared 24 participants with a high background caffeine intake (mean daily intake 313.54 mg) with a group with a low background intake (mean daily intake 45.76 mg) on a measure of backward recall. No statistically significant effects were reported, but there was a trend toward better overall recall performance in the high background consumption group. The only study to report any statistically significant effects of long-term caffeine consumption on human memory was a large-scale study by Jarvis[30] using a large sample of 7414 British adults. The measure of memory used was again a free recall task, this time preceded by incidental encoding, and it was found that there was a dose-response trend toward improved performance with higher levels of caffeine consumption. Unfortunately, however, the study did not control for acute ingestion of caffeine, so the effects of chronic consumption are potentially contaminated with short-term self-administered caffeine.

Other research has examined the effects of regular caffeine consumption on cognitive failures, which include problems remembering things. Research with a working sample,[31] a non-working sample[32], and an elderly sample[33] has shown that higher levels of regular caffeine consumption are associated with less frequent cognitive failures. Another approach has examined the effects of caffeine on consumers and non-consumers of caffeinated beverages.[34-36] These studies have usually focused on alertness, sustained attention and psychomotor speed, and there is a need to extend this methodology to consider semantic processing and executive function.

None of the studies described above produced any evidence of adverse effects of regular caffeine consumption, and given that acute effects on semantic memory and logical reasoning are universally positive, it was predicted that if any effects of long-term caffeine consumption on these tasks were found these would also be positive. As well as investigating the main effects of long-term caffeine consumption, the other primary aim of the present study was to investigate the possibility of an interaction between the level of long-term caffeine and an acute caffeine challenge to provide further data regarding the effects of caffeine withdrawal. The debate over the effects of caffeine withdrawal centres on whether acute ingestion of caffeine actually causes an improvement in cognitive performance or whether it merely restores degraded performance caused by pre-test abstinence from caffeine.[37-40] The present study required that participants abstain from caffeine for several hours before cognitive testing so that the effects of an acute caffeine challenge were not contaminated by the effects of self-administrated caffeine and was, therefore, in an ideal position to provide further

evidence to add to the debate. As James[37] suggests, if there is a withdrawal effect, it would have been expected that at baseline, consumers with a high regular caffeine intake would suffer relatively significant impairments in performance compared to low or non-consumers. Furthermore, after an acute caffeine challenge, it would be expected, if the caffeine withdrawal theory were correct, that there would be an interaction between acute and long-term consumption of caffeine, with an acute challenge improving (restoring) performance in participants who had high levels of regular caffeine consumption and not affecting those who were low caffeine users or non-users. If, however, as Smith[39] suggests, there is no caffeine withdrawal effect that causes impairment in performance, there should be no difference between high or low caffeine consumers at baseline and no interaction between long-term consumption of caffeine and the acute challenge.

Methodological Considerations

The present analysis collated and employed the data sets from previous studies[21,24,25], which used a caffeine dose of 4mg/kg in the acute caffeine challenge and methods of caffeine administration and measures of semantic memory that are known to produce consistent and replicable results. As long-term caffeine consumption results from self-administration, it is theoretically possible that mean daily caffeine intake is confounded with other variables such as personality factors, stress levels or health-related behaviours that might mediate caffeine consumption. A considerable volume of research has attempted to identify the correlates of caffeine consumption, and among the factors which have been identified as being positively correlated with caffeine consumption are smoking,[41] age,[42] work in managerial and administrative positions,[42] and extraversion.[16,43] Of these variables, only nicotine and age are known to influence memory performance, but as the participants were all full-time students and either non-smokers or occasional smokers, the effect of these variables was not considered to mediate caffeine intake in the sample used in the present experiment.

Hypotheses

Main effects of caffeine

A) Participants with a high level of regular caffeine consumption will perform better on the semantic memory test than low consumers.

B) Participants with a high level of regular caffeine consumption will perform better on the logical reasoning test than low consumers.

C) Acute ingestion of caffeine (4mg/kg) will significantly improve semantic memory performance; the number of trials attempted will be increased, the accuracy of responses will be increased, and mean reaction time (MRT) for correct responses will be decreased.

D) Acute ingestion of caffeine (4mg/kg) will significantly improve central executive function; the number of trials attempted will be increased, the accuracy of responses will be increased, and MRT for correct responses will be decreased.

Interactions between long-term and acute exposure to caffeine

There will be no statistically significant interactions between long-term (self-administered) exposure to caffeine and acute exposure to caffeine (4mg/kg).

METHOD

The research was approved by the ethics committee School of Psychology, Cardiff University, and carried out with the informed consent of the participants.

The study employed a between-subjects design with long-term caffeine consumption and experimental caffeine condition as between-subjects factors. Participants were divided into groups of differing background consumption based on mean daily caffeine intake, with comparison groups formulated in two ways. The first comparison groups for background consumption were derived statistically and consisted of four groups formed by a quartile split based on daily caffeine intake. The second comparison group attempted to address a more practical question and compared participants whose caffeine intake was less than or equal to 30mg daily (i.e. whose caffeine intake was, on average less than a cup of tea per day) and those whose caffeine intake was 30mg per day or above.

Participants

One hundred and seventy-seven participants were used in the analysis. All were non-smokers and regular caffeine consumers. (Twenty-three data sets out of 200 collected in three previous studies were discounted because demographic data was missing). The demographic details of the 177 participants that comprised the sample are shown in table 1. Participants were paid £20-25 for participation in the research.

Table 1: Participant demographics and personality characteristics (means, SEs in parentheses).

Age (years)	21.47 (0.29)
Mean daily caffeine consumption (mg)	137.83 (9.19)
EPI: Impulsivity (0-low to 9-high)	4.59 (0.15)
EPI: Sociability (0-low to 12-high)	7.58 (0.18)
EPI: Extraversion (0-low to 23-high)	12.67 (0.30)

Semantic memory

This task was based on Baddeley's[44] semantic memory task and was described in detail by Nguyen-Van-Tam and Smith.[21-25]

The exclusion criteria for this test were failure to attempt at least 50 trials at baseline and/or failure to get at least 80% of the trials correct.

7.2.8.2 Central executive function

This task was based on Baddeley's[45] logical reasoning task and was described in detail by Nguyen-Van-Tam and Smith.[21-25]

The exclusion criterion for the task was failure to provide correct verifications for at least 50% of the simple active statements in the baseline condition.

Analysis

As in our previous studies, individual differences in performance were controlled by using ANCOVA with performance data from the baseline condition as a covariate. The between-subjects groups were derived based on background daily caffeine consumption using quartile division and caffeine intakes of less than or equal to 30mg/24h or more than 30mg/24h.

Analysis of the data was undertaken in three stages.

1. A detailed description of the daily caffeine consumption of the participants in each data set so that comparisons can be made with the existing literature regarding daily caffeine intake.
2. Analysis of the baseline data to determine the effects of long-term caffeine self-administration in participants with differing levels of regular caffeine use.
3. Investigation of the interaction between level of long-term, self-administered caffeine and acute experimental caffeine condition.

RESULTS

Participants in the semantic memory data set: Three participants met the exclusion criteria; 174 complete data sets were analysed. The pattern of long-term, self-administered caffeine consumption among the participants who formed the semantic memory data set revealed a wide distribution of caffeine consumption which ranged from 0 mg/24h to 570 mg/24h (table 2). The mean daily caffeine consumption of the sample was 137.90 mg, equivalent to approximately 2-3 cups of instant coffee, and was lower than the UK average of 202 mg per day suggested by Fredholm, Bättig, Holmén, Nehlig and Zvartau[46] and considerably lower than the average UK daily caffeine intake of 359 mg suggested by Scott et al.[41]. The distribution of daily caffeine intake appeared to be approximately bimodal, with the highest frequencies occurring at 0-25mg/24h and 150-175mg/24h. Regular caffeine consumption for the different comparison groups is shown in table 3.

Table 2: Semantic memory data set: self-administered, daily caffeine consumption, mg/24h (n = 174).

Mean	137.90
SE.	9.33
Median	130.00
Range	570.00
Minimum	0.00
Maximum	570.00
Interquartile range	185.00

Table 3: Semantic memory data set: daily caffeine consumption and sample size for each comparison group (SEs in parentheses).

Formation of comparison groups	Group	Mean mg/24h	n
Quartile split	1st quartile	3.41 (1.31)	44
	2nd quartile	73.14 (5.64)	43
	3rd quartile	168.72 (3.80)	43
	4th quartile	305.57 (12.20)	44
≤ 30mg/24h or > 30mg/24h	≤ 30mg/24h	6.37 (1.54)	51
	> 30mg/24h	192.44 (9.55)	123

Participants in the logical reasoning data set

One hundred and sixty-seven complete data sets were analysed; 10 participants met the exclusion criteria. For the participants who formed the data set for the logical reasoning task, there was again a wide distribution of caffeine consumption (table 4). However, as for the semantic memory data set, average caffeine consumption appeared to be lower in this student

sample than in the UK population as a whole, according to the figures suggested by Scott et al.[41] and Fredholm et al.[46] As for the semantic data set, the distribution of chronic caffeine consumption showed an approximately bimodal distribution, with the highest frequencies occurring at 0-25 mg/24h and 150-175 mg/24h.

Long-term, self-administered caffeine consumption for each of the comparison groups is shown in table 5.

Table 4: Logical reasoning data set: self-administered, daily caffeine consumption, mg/24h (n = 167).

Mean	143.05
SE.	9.52
Median	130.00
Range	570.00
Minimum	0.00
Maximum	570.00
Interquartile range	185.00

Table 5: Logical reasoning data set: daily caffeine consumption and sample size for each comparison group (SEs in parentheses).

Formation of comparison groups	Group	Mean mg/24h	n
Quartile split	1st quartile	5.36 (1.60)	42
	2nd quartile	82.02 (5.80)	42
	3rd quartile	176.31 (3.51)	42
	4th quartile	312.56 (12.40)	43
≤ 30mg/24h, > 30mg/24h	≤ 30mg/24h	7.07 (1.68)	46
	> 30mg/24h	194.75 (9.58)	121

Effects of long-term consumption of caffeine in the baseline condition

Semantic memory

A series of one-way ANOVAs and t-tests were used to compare the performance of the comparison groups with differing regular caffeine intakes.

Comparison of groups with four different levels of regular caffeine consumption

In the baseline condition (prior to the acute challenge), there were no statistically significant differences on any indices of semantic memory performance between any groups formed by quartile division of participants by daily caffeine intake (table 6).

Table 6: Semantic memory, baseline: means for comparison groups formed by quartile division of participants by daily caffeine consumption (SEs in parentheses).

Index of performance	Group	Mean daily caffeine intake (mg)	Non-adjusted mean (SE.)
Number of trials attempted	1st quartile	3.41	112.89 (4.09)
	2nd quartile	73.14	121.70 (4.14)
	3rd quartile	168.72	114.72 (4.14)
	4th quartile	305.57	122.57 (4.09)
Percentage of trials correct	1st quartile	3.41	93.94 (0.59)
	2nd quartile	73.14	92.95 (0.60)
	3rd quartile	168.72	92.76 (0.60)
	4th quartile	305.57	93.61 (0.59)
MRT correct trials (msec)	1st quartile	3.41	1499.58 (57.23)
	2nd quartile	73.14	1399.95 (57.89)
	3rd quartile	168.72	1523.30 (57.89)
	4th quartile	305.57	1397.49 (57.23)

Comparison of low and non-consumers and regular caffeine consumers

It was found that there was no significant difference in any index of semantic memory performance between the group with a daily caffeine intake of less than or equal to 30mg/24h and the group with a daily caffeine intake of more than 30mg/24h (table 7).

Table 7: Semantic memory, baseline: means for comparison groups with caffeine intake of ≤ 30mg/24h or > 30mg/24h (SEs in parentheses).

Index of performance	Group	Mean daily caffeine intake (mg)	Non-adjusted mean (SE.)
Number of trials attempted	≤ 30mg/24h	6.37	115.67 (3.85)
	> 30mg/24h	192.44	118.92 (2.45)
Percentage of trials correct	≤ 30mg/24h	6.37	93.95 (0.42)
	> 30mg/24h	192.44	93.06 (0.38)
MRT correct trials (msec)	≤ 30mg/24h	6.37	1482.15 (57.09)
	> 30mg/24h	192.44	1443.75 (33.36)

Logical reasoning

The differences in performance on the logical reasoning task in the various comparison groups were tested using one-way ANOVAs and t-tests.

Comparison of groups with four different levels of regular caffeine consumption

As for semantic memory, it was found that in the baseline condition (prior to the acute challenge), there were no statistically significant differences between comparison groups for

any index of logical reasoning performance between any of the groups formed by quartile division of participants by daily caffeine intake (table 8).

Comparison of low and non-consumers and regular caffeine consumers

For the groups with daily caffeine intakes of less than or equal to 30mg/24h and more than 30mg/24h, there were no significant differences in performance on any index of the logical reasoning task (table 9).

Table 8: Logical reasoning, baseline: means for comparison groups formed by quartile division of participants by daily caffeine consumption (SEs in parentheses).

Index of performance	Group	Daily caffeine intake (mg)	Non-adjusted mean (SE.)
Number of trials attempted	1st quartile	5.36	60.21 (2.51)
	2nd quartile	82.02	57.64 (2.51)
	3rd quartile	176.31	55.69 (2.51)
	4th quartile	312.56	59.93 (2.54)
Percentage of trials correct	1st quartile	5.36	87.34 (1.51)
	2nd quartile	82.02	88.54 (1.51)
	3rd quartile	176.31	89.62 (1.51)
	4th quartile	312.56	90.29 (1.53)
MRT correct trials (msec)	1st quartile	5.36	3349.87 (179.12)
	2nd quartile	82.02	3546.22 (179.21)
	3rd quartile	176.31	3472.13 (179.12)
	4th quartile	312.56	3430.96 (181.29)

Table 9: Logical reasoning, baseline: means for comparison groups with caffeine intake of ≤ 30mg/24h or > 30mg/24h (SEs in parentheses).

Index of performance	Group	Daily caffeine intake (mg)	Non-adjusted mean (SE.)
Number of trials attempted	≤ 30mg/24h	7.07	57.46 (2.57)
	> 30mg/24h	194.75	54.92 (1.43)
Percentage of trials correct	≤ 30mg/24h	7.07	87.62 (1.42)
	> 30mg/24h	194.75	89.44 (0.89)
MRT correct trials (msec)	≤ 30mg/24h	7.07	3315.55 (148.87)
	> 30mg/24h	194.75	3500.10 (109.30)

SUMMARY

- When comparison groups with four different levels of long-term caffeine consumption were compared, there were no effects of regular caffeine consumption for any indices of semantic memory or logical reasoning performance.

- When two groups with regular caffeine consumption of ≤ 30mg/24h (equivalent to less than one cup of tea per day) and >30mg/24h were compared, there were no effects of the level of caffeine consumption for any indices of semantic memory or logical reasoning performance.

Long-term caffeine consumption and the experimental caffeine condition

Semantic memory

A series of ANCOVAs were conducted to determine whether there were any main effects of long-term caffeine consumption, experimental caffeine challenge condition or interactions between the two in the post-drink test session. The minimum cell size for the acute x chronic interaction was 20, where background caffeine consumption groups were divided into quartiles and 24, where background caffeine consumption was divided based on more or less than or equal to 30mg of caffeine per day.

Comparison of groups with four different levels of regular caffeine consumption

It was found that where a quartile split formed the groups with differing levels of long-term caffeine consumption, there were no main effects of long-term consumption and no interactions between long-term consumption and experimental caffeine condition (table 10). As expected, there were highly significant main effects of acute exposure to caffeine on the number of trials attempted $F(1, 165) = 15.22$, $MSe = 96.32$, $p < 0.0001$, percentage of trials correct, $F(1, 165) = 12.79$, $MSe = 9.01$, $p < 0.0001$ and MRT for correct trials, $F(1, 165) = 11.83$, $MSe = 18686.67$, $p < 0.0025$ (table 11).

Comparison of low and non-consumers and regular caffeine consumers

When the group of participants with background caffeine consumption of less than or equal to 30mg/24h were compared with those with background caffeine consumption of more than 30mg/24h, there were no main effects of level of regular caffeine consumption or interactions between long-term consumption and experimental caffeine condition (table 12). As in the previous analysis, there were the usual main effects of acute exposure to caffeine for the number of trials attempted $F(1, 169) = 10.65$, $MSe = 96.46$, $p < 0.0025$, percentage of trials correct, $F(1, 169) = 13.83$, $MSe = 8.85$, $p < 0.0001$ and MRT for correct trials, $F(1, 169) = 7.76$, $MSe = 18916.88$, $p < 0.01$.

Table 10: Semantic memory: adjusted and non-adjusted means for comparison groups formed by quartile division of participants by daily caffeine consumption in caffeine (4mg/kg) or placebo conditions (SEs in parentheses).

Index of performance	Group	Daily caffeine intake (mg)	Caffeine condition	Non-adjusted mean	Adjusted mean
Number of trials attempted	1st quartile	3.41	Caffeine	131.80 (6.65)	133.54 (2.20)
	2nd quartile	73.14		129.30 (5.16)	133.51 (2.20)
	3rd quartile	168.72		127.55 (5.69)	132.94 (2.10)
	4th quartile	305.57		133.08 (5.26)	130.76 (2.01)
	1st quartile	3.41	Placebo	119.79 (4.46)	127.03 (2.02)
	2nd quartile	73.14		140.04 (5.94)	129.86 (2.07)
	3rd quartile	168.72		124.48 (6.69)	125.02 (2.14)
	4th quartile	305.57		132.10 (6.72)	125.45 (2.20)
Percentage of trials correct	1st quartile	3.41	Caffeine	96.39 (0.54)	95.74 (0.67)
	2nd quartile	73.14		96.00 (0.65)	95.28 (0.67)
	3rd quartile	168.72		93.53 (0.77)	94.82 (0.65)
	4th quartile	305.57		95.24 (0.65)	95.10 (0.61)
	1st quartile	3.41	Placebo	93.41 (0.91)	93.05 (0.61)
	2nd quartile	73.14		92.66 (1.39)	93.83 (0.63)
	3rd quartile	168.72		94.15 (1.14)	93.72 (0.66)
	4th quartile	305.57		94.16 (0.95)	93.82 (0.67)
MRT correct trials (msec)	1st quartile	3.41	Caffeine	1293.95 (66.82)	1271.27 (30.58)
	2nd quartile	73.14		1284.47 (55.92)	1249.35 (30.59)
	3rd quartile	168.72		1369.54 (72.36)	1273.54 (29.35)
	4th quartile	305.57		1284.83 (67.76)	1295.43 (27.91)
	1st quartile	3.41	Placebo	1379.55 (60.02)	1335.14 (27.95)
	2nd quartile	73.14		1182.85 (52.28)	1293.13 (28.78)
	3rd quartile	168.72		1388.01 (98.08)	1380.24 (29.83)
	4th quartile	305.57		1238.90 (75.41)	1369.21 (30.72)

Table 11: Main effects of caffeine on (a) number attempted, (b) Percent correct and (c) Mean RT for correct sentences (msecs).

a.	*Caffeine (4mg/kg)*	*Placebo*
Adjusted mean(SE.)	132.69 (1.06)	126.84 (1.05)
Non-adjusted (SE.)	130.49 (2.81)	129.00 (3.03)
b.		
Adjusted mean(SE.)	95.23 (0.36)	93.60 (0.32)
Non-adjusted (SE.)	95.25 (0.35)	94.16 (0.95)
c. Adjusted mean(SE.)	1272.40 (14.84)	1344.43 (14.67)
Non-adjusted (SE.)	1308.54 (32.98)	1308.42 (36.51)

Table 12: Semantic memory: adjusted and non-adjusted means for comparison groups with daily caffeine intake of ≤ 30mg/24h or > 30mg/24h in caffeine (4mg/kg) or placebo conditions (SEs in parentheses).

Index of performance	Group	Daily caffeine intake (mg)	Caffeine condition	Non-adjusted mean	Adjusted mean
Number of trials attempted	≤ 30mg/24h	3.41	Caffeine	131.75 (6.30)	132.23 (2.01)
	> 30mg/24h	73.14		130.00 (3.07)	132.76 (1.25)
	≤ 30mg/24h	3.41	Placebo	124.07 (4.94)	127.72 (1.89)
	> 30mg/24h	73.14		131.18 (3.77)	126.57 (1.27)
Percentage of trials correct	≤ 30mg/24h	3.41	Caffeine	96.33 (0.46)	95.66 (0.61)
	> 30mg/24h	73.14		94.82 (0.44)	95.05 (0.38)
	≤ 30mg/24h	3.41	Placebo	93.64 (0.82)	93.30 (0.57)
	> 30mg/24h	73.14		93.52 (0.72)	93.71 (0.38)
MRT correct trials (msec)	≤ 30mg/24h	3.41	Caffeine	1303.20 (66.28)	1275.96 (28.09)
	> 30mg/24h	73.14		1310.61 (38.22)	1272.25 (17.52)
	≤ 30mg/24h	3.41	Placebo	1341.96 (59.24)	1326.21 (26.48)
	> 30mg/24h	73.14		1293.57 (45.85)	1350.24 (17.73)

Logical reasoning

To determine whether there were any main effects of acute exposure to caffeine, background consumption or interactions between the two, a series of ANCOVAs were performed. Where the background consumption groups were formed by quartile division based on daily caffeine consumption, the minimum cell size for the acute x chronic interaction was 19. When background consumption was divided by consumption of more or less than or equal to 30mg/24h, the minimum cell size for the acute x chronic interaction was 23.

Comparison of groups with four different levels of regular caffeine consumption

As for semantic memory, when the background consumption groups were derived by division into quartiles, there were no interactions between acute and chronic consumption that approached statistical significance (table 13).

Table 13: Logical reasoning: adjusted and non-adjusted means for comparison groups formed by quartile division of participants by daily caffeine consumption in caffeine (4mg/kg) or placebo conditions (SEs in parentheses).

Index of performance	Group	Daily caffeine intake (mg)	Caffeine condition	Non-adjusted mean	Adjusted mean
Number of trials attempted	1st quartile	5.36	Caffeine	61.86 (3.70)	60.36 (1.46)
	2nd quartile	82.02		52.00 (3.13)	59.33 (1.55)
	3rd quartile	176.31		56.14 (2.43)	59.53 (1.46)
	4th quartile	312.56		60.32 (4.19)	59.71 (1.42)
	1st quartile	5.36	Placebo	58.57 (3.72)	57.25 (1.46)
	2nd quartile	82.02		62.30 (3.89)	56.13 (1.41)
	3rd quartile	176.31		55.24 (3.03)	55.72 (1.46)
	4th quartile	312.56		59.47 (3.78)	59.17 (1.53)
Percentage of trials correct	1st quartile	5.36	Caffeine	88.43 (2.73)	89.35 (1.30)
	2nd quartile	82.02		91.37 (2.41)	91.59 (1.36)
	3rd quartile	176.31		93.51 (1.13)	92.93 (1.30)
	4th quartile	312.56		92.38 (1.85)	91.89 (1.27)
	1st quartile	5.36	Placebo	86.80 (2.13)	87.94 (1.30)
	2nd quartile	82.02		90.84 (1.65)	91.13 (1.24)
	3rd quartile	176.31		93.39 (1.41)	93.09 (1.29)
	4th quartile	312.56		91.28 (1.37)	89.98 (1.36)
MRT correct trials (msec)	1st quartile	5.36	Caffeine	2999.66 (168.49)	3118.98 (117.80)
	2nd quartile	82.02		3702.84 (281.01)	3148.27 (126.20)
	3rd quartile	176.31		3316.95 (154.48)	3239.02 (117.73)
	4th quartile	312.56		3242.82 (288.53)	3290.56 (115.00)
	1st quartile	5.36	Placebo	3204.26 (208.57)	3251.55 (117.70)
	2nd quartile	82.02		3154.37 (292.96)	3466.03 (113.32)
	3rd quartile	176.31		3350.10 (212.14)	3391.03 (117.70)
	4th quartile	312.56		3190.31 (254.87)	3169.08 (123.72)

As would be expected, there was a main effect of the experimental caffeine condition, with more trials being attempted in the caffeine condition than in the placebo condition, $F(1, 158) = 6.52$, $MSe = 44.54$, $p < 0.025$ (Adjusted means: Caffeine: 59.73 (0.74); Placebo: 57.07 (0.73)). There was a trend toward a reduced MRT for correct trials after acute exposure to caffeine. The average reaction time was 3319.42 (SE 59.13) msec after placebo as opposed to 3199.21 (SE 59.51) msec after caffeine, $F(1, 158) = 2.04$, $MSe = 290826.62$, $p = 0.078$ (one-tailed). Non-adjusted means were 3190.31 (SE 254.87) msec and 3305.36 (SE 116.56) msec, respectively. For the percentage of correct trials, it was found that there was a main effect of long-term caffeine consumption, $F(3, 158) = 3.85$, $MSe = 35.17$, $p < 0.025$. Post-hoc analysis using a series of Bonferroni t-tests revealed a statistically significant difference between the

first and third quartiles for the percentage of trials correct with those with a higher background caffeine intake outperforming those with a lower background intake (table 14).

Table 14: Logical reasoning, percentage of trials correct: adjusted and non-adjusted means for comparison groups formed by quartile division of participants by daily caffeine consumption (SEs in parentheses)

Comparison groups	Daily caffeine intake (mg/24h)	Non-adjusted mean	Adjusted mean
1st quartile	5.36 (1.60)	87.61 (1.72)	88.64 (0.92)
2nd quartile	82.02 (5.80)	91.08 (1.40)	91.36 (0.92)
3rd quartile	176.31 (3.51)	93.45 (0.89)	93.01 (0.92)
4th quartile	312.56 (12.40)	91.87 (1.17)	90.93 (0.92)

Comparison of low and non-consumers and regular caffeine consumers

When the group of participants with chronic, self-administered caffeine consumption of less than or equal to 30mg/24h was compared with the group with a chronic caffeine consumption of greater than 30mg/24h, it was again found that there were no main effects of level of long-term consumption or interactions with experimental caffeine condition that approached significance (table 15). For the number of trials attempted, a main effect of the experimental caffeine condition was found with an average of 57.23 (SE 0.82) trials attempted after placebo as opposed to 59.81 (SE 0.82) after caffeine, $F(1, 162) = 4.98$, $MSe = 44.27$, $p < 0.05$. Non-adjusted means were 58.96 (SE 1.81) and 57.75 (SE 1.75), respectively. The main effect of regular consumption was again statistically significant for the percentage of trials correct, with 89.78 (SE 0.73) per cent correct in the group with a caffeine consumption of < 30mg/24h and 90.90 (SE 0.73) per cent in the group with a caffeine consumption > 30mh/24h, $F(1, 162) = 8.14$, $MSe = 5695.36$, $p < 0.01$. Non-adjusted means were 88.02 (SE 1.59) after the placebo and 92.13 (SE 0.70) after caffeine.

Table 15: Logical reasoning: adjusted and non-adjusted means for comparison groups with daily caffeine intake of ≤ 30mg/24h or > 30mg/24h in caffeine (4mg/kg) or placebo conditions (SEs in parentheses).

Index of performance	Group	Daily caffeine intake (mg)	Caffeine condition	Non-adjusted mean	Adjusted mean
Number of trials attempted	≤ 30mg/24h	7.07	Caffeine	61.22 (3.41)	59.98 (1.39)
	>30mg/24h	194.75		56.42 (2.03)	59.65 (0.87)
	≤ 30mg/24h	7.07	Placebo	59.91 (3.62)	57.75 (1.39)
	> 30mg/24h	194.75		58.61 (2.10)	56.71 (0.85)
Percentage of trials correct	≤ 30mg/24h	7.07	Caffeine	88.86 (2.52)	89.70 (1.24)
	> 30mg/24h	194.75		92.43 (1.08)	92.11 (0.77)
	≤ 30mg/24h	7.07	Placebo	87.19 (1.97)	88.05 (1.24)
	> 30mg/24h	194.75		91.84 (0.89)	91.51 (0.76)
MRT correct trials (msec)	≤ 30mg/24h	7.07	Caffeine	3021.64 (155.12)	3146.50 (112.54)
	> 30mg/24h	194.75		3414.12 (148.18)	3224.37 (70.11)
	≤ 30mg/24h	7.07	Placebo	3133.62 (198.37)	3229.85 (112.48)
	> 30mg/24h	194.75		3257.94 (150.70)	3361.22 (69.17)

SUMMARY

- No interaction between the level of regular caffeine consumption and experimental caffeine condition was found for any index of semantic memory or logical reasoning performance.
- There was the usual profile of caffeine acute caffeine effects on semantic memory and logical reasoning tasks.
- On the logical reasoning task, after the acute caffeine challenge, high levels of regular, long-term caffeine consumption were associated with an increase in the percentage of trials correct.

DISCUSSION

The objectives of the study were to determine the effects of long-term, self-administered caffeine consumption on semantic memory and executive function and any possible interaction with the experimental caffeine conditions. It was found that the range of caffeine consumption for participants in both the semantic memory and executive function data sets varied considerably, with mean daily caffeine intakes of between 137-144mg/24h, considerably lower the mean daily caffeine intakes for the general population of the UK suggested by Scott et al.[41] and Fredholm et al.[46]

In the baseline test condition (before the acute caffeine challenge), there were no effects of the level of regular caffeine consumption for any index of semantic memory or logical reasoning performance using any of the comparison groups. This result suggests no effects of long-term caffeine self-administration on semantic memory and logical reasoning. The result is not perhaps entirely surprising as it is noted that the long-term physiological changes observed in animals as a result of regular caffeine consumption, which could potentially lead to changes in memory function, were obtained with much higher amounts of caffeine than are generally consumed by humans.

The finding that there is no effect of the level of regular caffeine consumption at baseline also provided further evidence to add to the caffeine withdrawal debate. If there were an effect of caffeine withdrawal, as suggested by James[37], it would be expected that participants with a high level of regular caffeine consumption would, after an abstinence of approximately 8 hours, have impaired performance compared to low or non-consumers for whom caffeine withdrawal effects would be less relevant. This outcome was clearly not observed as there were no differences in performance between participants with differing levels of regular caffeine consumption, including those who were very low or non-consumers and those who were regular consumers. It is noted, however, that the study required that participants abstain from self-administered caffeine for only 8 hours prior to testing and that the withdrawal effect may not have been at its maximum. (For self-reported affective symptoms Daly and Fredholm[47] suggest withdrawal effects reach a peak at 20-48 hours). It is also noted that the student samples used in the experiment had a considerably lower caffeine intake than the general population. The sample may have been intrinsically less prone to withdrawal effects than a sample whose daily intake is more typical of the general population. Given these potential shortcomings, it is suggested that whilst the study goes towards addressing the issue of caffeine withdrawal on semantic memory and executive function, further experimentation may be necessary before any definitive conclusions can be reached.

No statistically significant interactions between long-term caffeine consumption and experimental caffeine condition were found for any performance index for the semantic memory or logical reasoning task. However, as expected, there was the usual profile of caffeine effects after the acute caffeine challenge. Somewhat unexpectedly, it was also found that for the logical reasoning task, there was also a main effect of long-term caffeine consumption for the percentage of trials correct, with participants with high levels of regular

consumption outperforming those with lower levels of long-term consumption. This effect was not reported at baseline, and it would seem possible that long-term caffeine consumption may mediate learning of this task, which is known to be subject to practice effects.

In summary, the results of the study show the familiar profile of caffeine effects after an acute caffeine challenge but no effects of level of long-term consumption apart from in the test session on the logical reasoning task, which may indicate a possible effect of caffeine on learning. It is acknowledged, however, that the findings regarding caffeine withdrawal must be treated with some caution due to the time for which caffeine was withdrawn prior to the experiment and the moderate caffeine consumption habits of the sample. In order to overcome these shortcomings, further research is required to investigate the issue of caffeine withdrawal on semantic memory and executive function using a sample with more typical caffeine consumption habits and an experimental procedure purposely designed to address the caffeine withdrawal issue.

REFERENCES

1. Lieberman HR. Caffeine. In: Handbook of Human Performance, Vol.2: Health and performance. (eds) A. P. Smith & D. M. Jones. London: Academic Press, 1992: 49-72.
2. Smith AP. Effects of caffeine on human behavior. Food Chem Toxicol, 2002; 40: 1243-55.
3. Smith AP. Caffeine. In: Nutritional Neuroscience. Edited by H. Lieberman, R. Kanarek and C Prasad, 2005; 335-359. London: Taylor & Francis.
4. Glade MJ Caffeine – Not just a stimulant. Nutrition, 2010; 26: 932-938.
5. Smith AP. Caffeine: Practical implications. In: Diet, Brain, Behavior: Practical Implications. Eds: R.B. Kanarek & H.R. Lieberman. Taylor & Francis. 2011; 271-292.
6. Doepker C, Lieberman H, Smith AP, Peck J, El-Sohemy A, Welsh B. Caffeine: Friend or Foe? Annual Review of Food Science and Technology, 2016; 7: 6.1–6.22. doi: 10.1146/annurev-food-041715-033243.
7. Smith AP The psychobiological processes underpinning the behavioural effects of caffeine. In: P. Murphy (ed), Routledge International Handbook of Psychobiology. London New York: Routledge. ISBN: 978-1-138-18800-6 (hbk) ISBN: 978-1-315-64276-5 (ebk), 2019; 239-250.

8. Nguyen-van-Tam DP, Smith AP. Caffeine and human memory: a literature review and some data. 19th International Scientific Colloquium on Coffee, 2001. Trieste. Association Scientifique Internationale du Café.
9. Smith AP, Kendrick, AM, Maben, AL. Effects of breakfast and caffeine on performance and mood late in the morning and after lunch. Neuropsychobiology, 1992; 26: 198-204.
10. Smith, AP, Brockman P, Flynn R, Maben AL, Thomas M. Investigation of the effects of coffee on alertness and performance and mood during the day and night. Neuropsychobiology, 1993; 27: 217-223.
11. Smith AP, Kendrick AM, Maben AL, Salmon, J. Effects of breakfast and caffeine on cognitive performance, mood and cardiovascular functioning. Appetite 1994; 22(1): 39-55.
12. Smith AP, Whitney H, Thomas M, Perry K, Brockman P. Effects of caffeine on mood, performance and cardiovascular functioning. Human Psychopharmacology-Clinical and Experimental 1997; 12(1): 27-33.
13. Smith AP, Sturgess W, Gallagher J. Effects of low dose caffeine given in different drinks on mood and performance. Human Psychopharmacology-Clinical and Experimental 1999; 14: 473-482.
14. Loke WH, Hinrichs JV, Ghoneim MM. Caffeine and diazepam: separate and combined effects on mood and memory and psychomotor performance. Psychopharmacology 1985; 87: 344-350.
15. Loke WH. Effects of caffeine on mood and memory. Physiology and Behavior 1988; 44(3): 367-372.
16. Mitchell PJ, Redman JR. Effects of caffeine, time of day and user history on study-related performance. Psychopharmacology 1992; 109(1-2): 121-126.
17. Barraclough MS, Foreman N. Factors influencing recall of supraspan word lists: caffeine dose and introversion. Pharmacopsychoccologia 1994; 7: 229-236.
18. Rogers PC, Dernoncourt C. Regular caffeine consumption: a balance of adverse and beneficial effects for mood and psychomotor performance. Pharmacology, Biochemistry and Behavior 1998; 59(4): 1039-1045.
19. Terry WS, Phifer B. Caffeine and memory performance on the AVLT. Journal of Clinical Psychology 1986; 42: 860-863.
20. Gupta U. Differential effects of caffeine on free recall after semantic and rhyming tasks in high and low impulsives. Psychopharmacology 1991; 105(1): 137-140.

21. Nguyen-Van-Tam DP, Smith AP. Caffeine, mood, verbal reasoning, semantic processing and levels of processing: An investigation of state dependent memory. World Journal of Pharmaceutical Research, 2022; 11(13): 2166-2190. doi: 10.20959/wjpr202213-25780
22. Nguyen-Van-Tam DP, Smith AP. The effect of everyday caffeine consumption on reports of attention and memory performance in different age groups: A preliminary investigation. World Journal of Pharmaceutical Research, 2022; 11(15): 34-52. doi: 10.20959/wjpr202213-26018
23. Nguyen-Van-Tam DP, Smith AP. Caffeine, memory, impulsivity and time of day. European Journal of Pharmaceutical and Medical Research, 2022; 9(12): 99-105.
24. Nguyen-Van-Tam DP, Smith AP. Caffeine, semantic processing, logical reasoning, implicit memory, recognition memory, and allocation of memory resources. World Journal of Pharmaceutical Research, 2023; 12(2): 1-28. doi: 10.20959/wjpr20232-26897
25. Nguyen-Van-Tam DP, Smith AP. Further investigation of the effects of caffeine on implicit memory, allocation of memory resources, semantic memory and executive function. World Journal of Pharmacy and Pharmaceutical Studies, 2023; 12(2): 1564-1584. doi: 10.20959/wjpps20232-24227
26. Fredholm BB. Adenosine actions and adenosine receptors after 1 week treatment with caffeine. Acta Physiologica Scandinavica, 1982; 115: 283-286.
27. Fastbom J, Fredholm BB. Effects of long-term theophylline treatment on adenosine A1-receptors in rat brain: autoradiographic evidence for increased receptor number and altered coupling to G-proteins. Brain Research, 1990; 507: 195-199.
28. Nakamoto T, Roy G, Gottschalk SB, Yazdani M, Rossowska M. Lasting effects of early chronic caffeine feeding on rats' behaviour and brain in later life. Physiology and Behavior, 1991; 49: 721-727.
29. Smith BD, Davidson RA, Green RL. Effects of caffeine and gender on physiology and performance: further tests of a biobehavioral model. Physiology and Behavior, 1993; 54: 415-422.
30. Jarvis MJ. (1993). Does caffeine intake enhance absolute levels of cognitive performance? Psychopharmacology, 1993; 110(1-2): 45-52.
31. Smith AP. Caffeine at work. Human Psychopharmacology Clinical and Experimental, 2005; 20: 441-445.
32. Smith AP. Caffeine, cognitive failures and health in a non-working community sample. Human Psychopharmacology: Clinical and Experimental, 2009; 24: 29-34.

33. Smith AP. Caffeine and health and cognition in the elderly. "Food supplements and cognition in healthy aging." A special issue of the Current Topics in Nutraceutical Research to celebrate life of Prof. Keith A. Wesnes (1950-2020). 2021; Supplement 1, pp. S1–S6. doi: https://doi.org/10.37290/ctnr2641–452X.19:S1–S6
34. Hewlett PJ, Smith AP. Acute effects of caffeine in volunteers with different patterns of regular consumption. Human Psychopharmacology Clinical and Experimental, 2006; 21: 167-180.
35. Smith, AP, Christopher G, Sutherland D. Effects of caffeine in overnight-withdrawn consumers and non-consumers. Nutritional Neuroscience, 2006; 9: 63-71.
36. Smith AP, Christopher G, Sutherland, D. Acute effects of caffeine on attention: A comparison of non-consumers and withdrawn consumers. Journal of Psychopharmacology, 2013; 27: 77-83. doi: 10.1177/0269881112460112
37. James JE. Does caffeine enhance or merely restore degraded psychomotor performance? Neuropsychobiology, 1994; 30: 124-125.
38. James JE. Acute and chronic effects of caffeine on performance, mood, headache and sleep. Neuropsychobiology, 1998; 38: 32-41.
39. Smith AP. Caffeine, caffeine withdrawal and performance efficiency. In B. S. Gupta & U. Gupta (Eds.), Caffeine and Behavior Current Views and Research Trends, 1999, pp. 161-178. Boca Raton: CRC Press.
40. Warburton DM. Effects of caffeine on cognition and mood without caffeine abstinence. Psychopharmacology, 1995; 119(1): 66-70.
41. Scott NR, Chakarobarty J, Marks V. Caffeine consumption in the United Kingdom: a retrospective survey. Food Sciences and Nutrition, 1989; 42F: 183-191.
42. Jacobson BH, Bouher BJ. Caffeine consumption by selected demographic variables. Health Values, 1991; 15: 49-55.
43. Landrum RE. College students' use of caffeine and its relationship to personality. College Student Journal, 1992; 26(2): 151-155.
44. Baddeley AD. The cognitive psychology of everyday life. British Journal of Psychology 1981; 72: 257-269.
45. Baddeley AD. A three-minute reasoning test based on grammatical transformation. Psychonomic Science 1968; 10: 341-342.
46. Fredholm BB, Bättig K, Holmén J, Nehlig A, Zvartau EE. (1999). Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. Pharmacological Reviews, 1999; 51(1): 83-133.

47. Daly JW, Fredholm, BB. Caffeine - an atypical drug of dependence. Drugs and Alcohol Dependence, 1998; 51: 199-206.