5-3-2021

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Recommended Citation

Berg, J., Cooper, J., Salonikas, C., Seyedsadjadi, N., & Grant, R. (2021). Acute caffeine intake in humans reduces post exercise performance in learning and memory. *Human Psychopharmacology: Clinical & Experimental, 36*(3), e2775. https://doi.org/10.1002/hup.2775

Acute caffeine intake in humans reduces post exercise performance in learning and memory

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ABSTRACT

Objective: To clarify the acute effect of caffeine on postexercise memory and learning performance.

Methods: Eight male slow-to-normal caffeine metabolizers, unhabituated to caffeine, were recruited into this randomized, double blind, placebo controlled, cross over study. Caffeine (150 mg) or the placebo was consumed one hour prior to two 30 min submaximal cycling sessions. Blood was collected at the beginning, after 20 and 35 min of exercise and 30 min postexercise. Mature brain-derived neurotrophic factor (BDNF) and proBDNF concentrations were determined. Auditory memory was assessed immediately, 30 min and 24 h postexercise.

Results: Participants averaged lower scores in every measure of learning and memory after ingesting caffeine compared to the placebo. Although the mean did not differ significantly for all measures, significant differences were found between the caffeine and placebo groups for the three indices; learning over time, short-term index and retroactive interference. The ratio of serum mBDNF:proBDNF increased with exercise across all time points. No significant difference in the mBDNF: proBDNF ratio was observed between treatment groups.

Conclusion: The consumption of caffeine prior to exercise may impair an unhabituated individual's capacity to learn and recall auditory information postexercise. However, it is yet to be elucidated whether this is through caffeine's modulating effects on brain BDNF.

INTRODUCTION

Caffeine, chemically known as 1,3,7-trimethylxanthine, was first isolated as a pure compound from coffee beans by Friedlieb Ferdinand Runge in 1819 (Waldvogel, 2003). Present in many plant species, caffeine is naturally found in coffee and a variety of teas as well as chocolate; and is frequently added to carbonated beverages, energy drinks, sports gels, supplements as well as some medications. Consequently, caffeine is the most commonly consumed drug in the world, ingested by approximately 80% of the global adult population at a dosage of about 220 mg per day (Fitt, Pell, & Cole, 2013; Australian Bureau of Statistics, 2015; Fulgoni, Keast, & Lieberman, 2015; Fulgoni et al., 2015; Heckman, Weil, & Gonzalez de Mejia, 2010). The large-scale consumption of caffeine is in part driven by its mental and physical stimulatory effects (Del Coso, Muñoz, & Muñoz-Guerra, 2011; Grosso, Godos, Galvano, & Giovannucci, 2017; Soar, Chapman, Lavan, Jansari, & Turner, 2016; El Yacoubi et al., 2000).

These effects are the result of caffeine's structural similarity to adenosine which, following consumption, facilitates its binding and thereby blockage of A1 and A2a adenosine receptors in both peripheral and central nervous system (CNS) tissue (Fredholm, 1979). Within the brain striatum, A1 and A2a receptors form functionally active heteromeric complexes with dopamine receptors (Fuxe et al., 2005; Ferré, 2010, 2016). Following passive diffusion across the blood brain barrier, caffeine binds to A1 and A2a receptors, antagonizing adenosine's inhibitory action while indirectly promoting dopamine's stimulatory action on psychomotor activity (Papeschi, 1972). In a similar fashion caffeine has also been shown to promote the release of other motor-activating neurotransmitters including glutamate and acetylcholine (Brown, James, Reddington, & Richardson, 1990; Carter, O'Connor, Carter, & Ungerstedt, 1995; Ciruela et al., 2006; Solinas et al., 2002).

While caffeine's function as an adenosine-receptor antagonist is thought to primarily drive its stimulatory effects, evidence suggests that caffeine-induced improvements in exercise performance may also be the result of enhanced free fatty acid utilization (Acheson et al., 2004), and calcium ion release, facilitating amplified skeletal muscle contractions (Olorunshola & Achie, 2011). Through these mechanisms, and those discussed above, caffeine has been shown to enhance performance during many types of exercise, including those that involve both strength and aerobic endurance (Burke, 2008; Warren, Park, Maresca, McKibans, & Millard-Stafford, 2010). However, some evidence suggests that caffeine's ubiquitous use as an ergogenic aid (Burke, 2008; Cook, Crewther, Kilduff, Drawer, & Gaviglio, 2011; Hurley, Hatfield, & Riebe, 2013; Motl et al., 2003; Stuart, Hopkins, Cook, & Cairns, 2005) by both athletes and non-athletes may inadvertently undermine one of exercises most well documented benefits, that being improved cognition.

The positive effects of exercise on several cognitive domains including memory are well documented, being observed in young, middle-aged and older adults both with and without dementia (Loprinzi, Frith, Edwards, Sng, & Ashpole, 2018; Northey, Cherbuin, Pumpa, Smee, & Rattray, 2018; Zheng, Xia, Zhou, Tao, & Chen, 2016). While several mechanisms are likely responsible, the demonstrated rise in brain-derived neurotrophic factor (BDNF) concentrations in response to exercise is thought to play a foundational role (Szuhany, Bugatti, & Otto, 2015). BDNF is a member of the neurotrophin family of growth factors. Its key role in neuronal growth and survival,

as well as synaptic plasticity, is mediated by varying levels of mature BDNF (mBDNF) and its precursor, proBDNF (Niculescu et al., 2018).

Current research surrounding BDNF's roles in memory and learning, as well as its potential as a therapeutic agent, tends to focus on the actions of mBDNF and often neglects the fact that proBDNF has its own, often opposing actions. For example, while mBDNF activates tropomyosin receptor kinase B (TrkB) to facilitate synaptic transmission (Ohira & Hayashi, 2009), proBDNF exerts inhibitory effects at synapses via activation of p75 neurotrophin receptors (p75NTRs) (Woo et al., 2005). Importantly, TrkBs have a widespread distribution in the hippocampus, particularly at cholinergic synapses (Sebastiiao et al., 2011), where they are activated by mBDNF to increase neurotransmitter release at active synapses, thus promoting the expression of long-term potentiation (LTP) (Cunha, Brambilla, & Thomas, 2010). This is thought to underpin the role of mBDNF in promoting neuronal growth and synaptic potentiation (Cho et al., 2013). On the other hand, activation of p75NTRs by proBDNF is thought to mediate synaptic retraction and neuronal death (apoptosis) via the facilitation of long-term depression (Borodinova & Salozhin, 2017; Underwood & Coulson, 2008).

Importantly (1) enhancement of LTP by mBDNF requires adenosine A2A receptor activation by endogenous adenosine (Fontinha, Diógenes, Ribeiro, & Sebastião, 2008) and (2) A2A receptor antagonists have been shown to significantly reduce brain mBDNF levels (Potenza et al., 2007). Thus caffeine, by acting as an adenosine antagonist, theoretically may adversely affect memory by reducing both the availability of mBDNF as well as the magnitude of the LTP it induces. This could at least partially explain previous reports of the negative effects of caffeine ingestion on both short and long-term memory (Childs & de Wit, 2006; Cupo, 2012; Han et al., 2007; Klaassen et al., 2013). However, in contrast to the studies referenced above there are some reports of beneficial effects, where caffeine ingestion generally improved performance on working memory tasks (Haller 2013).

In order to help clarify the effect of caffeine on memory we assessed nine indices of auditory learning and memory post exercise after the consumption of a physiologically relevant dose of caffeine or placebo control. We also quantified serum mBDNF and proBDNF levels to further our understanding of the potential mechanisms involved.

METHODS

Participants: This was a randomized, double blind, placebo controlled, cross over study. Fourteen healthy males aged between 47 and 64 years were initially recruited from the Northern Suburbs of Sydney, Australia. Of these only 8 were found to meet the strict inclusion and exclusion criteria. All participants (n = 8) were slow-normal caffeine metabolizers (CYP1A2 phenotyping described below), non-smokers, with a BMI of 18.5–30.0 kg/m2. Participants were untrained, performing less than 60 min/week of moderate physical activity. To ensure participants were capable of performing the moderate physical activity required for the study, each was required to return a normal electrocardiogram on a submaximal stress test. Individuals who had a diagnosis of diabetes or dementia or consumed more than three standard glasses of alcohol per week were excluded. Of the eight participants, six reported consuming less than one cup of coffee per week as part of their regular diet. The remaining two participants reported ingesting one cup of coffee per day. All participants were requested to avoid consumption of caffeinated food and beverages 2 weeks prior to and for the duration of the Experimental Procedure. Participants were reminded when to initiate the caffeine free diet and adherence was verbally confirmed at each experimental session. Ethical approval was obtained from The Adventist HealthCare Limited Ethics Committee, Australia (EC00141; #2017-010). Written informed consent was obtained from all participants.

CYP1A2 phenotyping: In order to determine participants' caffeine metabolism rate, each underwent CYP1A2 phenotyping. To do this, participants were asked to avoid consumption of caffeinated food and beverages for 24 h before ingestion of a 150 mg caffeine tablet. After 6 h blood was collected, centrifuged at 12,000 rpm for 10 min and frozen at −50°C. Paraxanthine/caffeine (Px:Ca) ratios were then determined using solid-phase extraction (SPE) and reverse phase high-performance liquid chromatography (HPLC). The desired metabolites were extracted from each serum sample using Strata-X polymeric SPE sorbents (Phenomenex Pty Ltd, Lane Cove West, NSW 2066) as described by Moret, Hidalgo, and Sanchez (2012). Samples were then vortexed and centrifuged for 10 min at 24,192 RCF and the organic layer was transferred to a separate tube before it was dried under a stream of nitrogen gas at 45°C. The residue was reconstituted and 50 µl was injected into the HPLC system (Shimadzu LC-10A VP, equipped with SPD-10A UV detector). Based on a study conducted by Urry, Jetter, and Landolt (2016) the Px:Ca cutoff for CYP1A2 activity was set as 0.55. Participants who returned an average Px:Ca ratio greater than 0.55 were considered to have high CYP1A2 inducibility and thus were excluded from the study.

Exercise experimental procedure: The experiment was a randomized, double-blinded, placebo-controlled crossover study. Participants were asked to present fasted for three exercise sessions—one practice submaximal exercise test and two experimental sessions. Participants were encouraged to aim for at least 6.5–8 h of sleep the night before each session, and to abstain from exercise at least 24 h prior to testing. A low fat 1 MJ carbohydrate meal was provided for breakfast 90 min prior to each of the two experimental sessions. Sixty minutes before each experimental session participants ingested either a capsule containing 150 mg of caffeine or a psyllium husk placebo. Each exercise session was undertaken between 8:00 a.m.–10:00 a.m. and the two experimental sessions were completed at least 7 days apart.

Submaximal exercise test: In order to determine the appropriate power output for use during the two experimental sessions participants underwent a graded submaximal exercise test on a cycle ergometer (Monark 828E) using the YMCA 12 Submaximal Cycle Ergometer Protocol (Golding, Myers, & Sinning, 1989). Height, weight, resting heart rate (HR) and resting blood pressure (BP) were recorded. A practice Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964) which assesses memory and learning (described in detail below) was also administered.

Experimental sessions: Participants ingested either the caffeine or placebo capsule one hour prior to each experimental session. The exercise protocol during each session included a 5-min warm-up and cool-down period of cycling (30% VO2Max), as well as 30 min of cycling at 70% VO2Max. Resting HR and BP was measured 30 min before and immediately prior to exercise commencement. HR was also recorded every minute during exercise, and ratings of perceived exertion (Borg, 1998) were recorded every 5 min. Blood samples were collected via a venous cannula at the beginning of exercise (T0), after 20 min of exercise (T20), after 35 min of exercise (T35), and 30 min postexercise (T65). These samples were immediately centrifuged and frozen on dry ice and then stored in liquid nitrogen until analysis. Memory and learning were assessed upon completion of each exercise session, as well as 30 min and 24 h postexercise using the RAVLT (described below).

Assessment of memory & learning: Memory and learning were assessed using the RAVLT (Rey, 1964). Immediately after exercise participants were read a 15-word list (List A) five times (trials 1–5) and asked to recall as many words as possible, in any order, after each trial. Participants were then read a different list of 15 words (List B) and again asked to recall as many words as possible (trial B), before being tested on List A once more (trial 6). Participants were also tested on List A, 30 min after completion of the first test (delayed recall). Then approximately 24 ± 1 h later, participants were read a 50-word list containing words from List A and List B, as well as 20 unrelated words that had

not been previously tested. Participants had to state whether they thought each word was from List A, List B or neither (24-h recognition). List A and List B of the original stimulus set developed by Taylor (1959) was used in the practice session (submaximal exercise test). In the two experimental sessions Form A and B developed by Shapiro and Harrison (1990) (SH Form A and SH Form B) were administered. These Forms have been shown to be of equal difficulty (Hawkins, Dean, & Pearlson, 2004). Importantly the order of Form administration was alternated to prevent practice effects. In this way half of the participants who ingested caffeine were tested using SH Form A first and the other half were administered SH Form B first. In each instance the test was administered and scored by the same examiner. Performance scores were then calculated as outlined in the RAVLT test manual (Schmidt, 1996) and indicated below.

Learning Over Time—sum of raw scores from trials 1–5 (/75). Reflects participants' capacity to comprehend and recall new information. Delayed Recall—raw score from the 30 min delayed recall trial (/15). Refers to the ability to recall specific information after a certain period of time, in this case 30 min. 24-Hour Recognition—total number of words correctly identified as being from List A or List B in the 24-h trial (/30). Indicates how well participants were able to recognize information previously encountered; a measure of short-term memory consolidation. Forgetting—delayed recall raw score divided by trial 6 raw score (/1). Demonstrates failure to recall learned information. Short-term Index—sum of raw scores from trials 1, 2 and B (/45). Reflects short-term ability to learn and recall new information. Long-term Index—sum of raw scores from trials 3, 4, 5, 6 and delayed recalled (/75). Indicates long-term ability to learn and recall new information. Proactive Inhibition—trial B raw score divided by trial 1 raw score (/1). Refers to the tendency of prior learning to impede present learning and recall. Retroactive Interference—(trial 5 raw score minus delayed recall raw score) divided by trial 5 raw score (/1). Reflects the tendency for recently learned information to interfere with the recall of previously learned information. Retrieval efficiency—delayed recall raw score divided by 24-h recognition raw score (/1). Demonstrates participants' ability to recall or retrieve information that has already been encoded and stored in the brain (remembering).

BDNF quantification: Serum mature and pro brain derived neurotrophic factor (mBDNF; proBDNF) concentrations were quantified using commercial enzyme- linked immunosorbent assays (SK00752-01 & SK00752-06 respectively; Aviscera Bioscience) according to the manufacturer's instructions. The manufacturer claims < 1% cross-reactivity for recombinant human proBDNF, which is low in comparison to other available ELISA kits. BDNF levels are expressed as percentage change (% change) from baseline. Results for 6 sets of blood samples (placebo and caffeine; T0, T20, T35, and T65) are presented. Two sets of blood samples were excluded due to hemolysis of a number of samples in either the placebo or caffeine condition.

Statistical analysis: Data was analyzed using SPSS version 24.0 and Graphpad Prism 8 for Windows. Prior to hypothesis testing, the Shapiro-Wilk test and histogram visualization were used to evaluate the assumption of normality. The influence of caffeine on exercise-induced changes in BDNF (mature and pro) was analyzed using repeated measures two- way analysis of variance (ANOVA) with Sidak's multiple comparisons post-hoc test. Differences in memory and learning scores between caffeine and control experimental sessions were assessed using paired t-tests.

RESULTS

Physiological marker: The average age of participants was 56 ± 8 years, range 47 to 64 years. All participants were considered to be in general good health and had an average BMI of 25.8 ± 3.0 kg/m2 and a systolic and diastolic BP of 134 ± 7 and 88 ± 5 mmHg respectively. Maximal aerobic capacity (VO2Max) (i.e., the maximum capacity of the heart to deliver blood to the muscles) was

30.8 ± 5.6 ml/kg/min (Table 1). The mean paraxanthine/caffeine (Px:Ca) ratio, an indicator of the rate that caffeine is metabolized, was 0.32 ± 0.15 (Table 2).

Post exercise performance on learning and memory measures: Performance on various learning and memory measures was assessed by interpreting the raw scores from each RAVLT trial as described above. For each of the measures, except for proactive inhibition and retroactive interference, a higher score indicates superior performance. Proactive inhibition and retroactive interference are scored out of one with a score of one indicating maximal inhibition or interference. Thus, a lower score indicates superior performance in these two measures. Conversely, a lower score in the forgetting and retrieval efficiency measures (also scored out of one) indicates inferior performance. As shown in Table 2, it was observed that participants averaged lower scores in every measure of learning or memory after ingesting the caffeine capsule compared to the placebo. Although the mean did not differ significantly for all test measures, significant differences were found between the caffeine and placebo treatment groups for three; learning over time (49.88 ± 17.63 vs. 55.88 ± 3.31, p = 0.016, n = 8), short-term index (21.5 ± 2.18 vs. 25.25 ± 1.68, p = 0.009, n = 8), and retroactive interference (mean = 0.27 ± 0.09 vs. 0.14 ± 0.06, p = 0.047, n = 8). No significant differences were observed between the caffeine and placebo treatment groups for delayed recall, 24-h recognition, forgetting, long-term index, proactive inhibition, and retrieval efficiency (Table 2).

TABLE 1 Physiological measures

	Mean (SD) (n = 8)
Age (years)	56 (8)
BMI (kg/m^2)	25.8 (3.0)
Systolic blood pressure (BP; mmHG)	134 (7)
Diastolic BP (mmHG)	88 (5)
Px:Ca (ratio)	0.32 (0.15)
VO_{2Max} (ml/kg/min)	30.8 (5.6)

TABLE 2 Memory and learning scores from the Rey Auditory Verbal Learning Test immediately postexercise

	Caffeine Mean (SEM)	Placebo Mean (SEM)
Learning over time*	49.88 (17.63)	55.88 (3.31)
Delayed recall	9.63 (1.53)	11.25 (1.10)
24-h recognition	17.88 (1.67)	19.50 (1.41)
Forgetting	0.86 (0.06)	1.00 (0.04)
Short-term Index**	21.50 (2.18)	25.25 (1.68)
Long-term index	54.00 (5.79)	59.63 (3.99)
Proactive inhibition	0.90 (0.14)	0.74 (0.08)
Retroactive interference*	0.27 (0.09)	0.14 (0.06)
Retrieval efficiency	0.55 (0.08)	0.57 (0.04)

Abbreviation: SEM, standard error of the mean.

*$p < 0.05$, **$p < 0.01$, $n = 8$.

Serum mBDNF and proBDNF levels before, during and after exercise: We then sought to determine if BDNF levels altered during exercise in response to caffeine ingestion. To do this we quantified serum mBDNF and proBDNF levels at four time points; before (time 0 min,T0), during (time 20 min from

baseline, T20; time 35 min from baseline, T35) and 30 min post exercise (time 65 min from baseline, T65), for both the caffeine and placebo treatments. As shown in Table 3 and Figure 1, there was a significant steady increase in mBDNF levels during and after exercise following the ingestion of 150 mg of caffeine. Specifically total serum mBDNF levels were 22.92 ± 6.02% ($F = 19.72$, $p < 0.05$, $n = 6$), 36.86 ± 7.35% ($F = 19.72$, $p < 0.05$, $n = 6$) and 37.72 ± 6.18% ($F = 19.72$, $p < 0.05$, $n = 6$) higher at T20, T35 and T65 than at baseline (T0). While no significant percent change in proBDNF levels was found at any time point, when the ratio of mBDNF:proBDNF was considered a significant increase during exercise following the ingestion of caffeine was again observed. The ratio of mBDNF:proBDNF increased by 23.70 ± 5.70% ($F = 11.56$, $p < 0.01$, $n = 6$), 35.25 ± 7.44% ($F = 11.56$, $p < 0.001$, $n = 6$), and 36.48 ± 7.98% ($F = 11.56$, $p < 0.001$, $n = 6$) at T20, T35 and T65 respectively (Table 3, Figure 2). After ingestion of the placebo, a significant increase in mBDNF was only observed at T35 when compared to baseline (% change = 28.74 ± 4.47, $F = 19.72$, $p < 0.01$, $n = 6$). As with the ingestion of caffeine no significant percent change in proBDNF levels was found at any time point. However when the ratio of mBDNF: proBDNF was considered a significant increase during exercise following the ingestion of the placebo was found. Specifically the ratio of mBDNF:proBDNF increased by 21.55 ± 5.15% ($F = 11.56$, $p < 0.05$, $n = 6$) and 28.20 ± 4.22% ($F = 11.56$, $p < 0.01$, $n = 6$) at T20 and T35. However no significant increase in mBDNF:proBDNF was found at T65 (Table 3, Figure 2). No significant difference in mBDNF, proBNDF or the ratio of mBDNF:proBDNF was observed between treatment groups (i.e., caffeine vs. placebo) at any time point.

DISCUSSION

The primary aim of this study was to clarify the effect of caffeine on auditory learning and memory following moderate exercise in a cohort of middle-aged men in general good health who were unhabituated to caffeine. We observed that compared to placebo, the ingestion of a 150 mg of caffeine one hour prior to exercise reduced postexercise learning and memory capacity across multiple domains. Statistically significant differences between placebo and caffeine treatments were observed for reduced learning over time, short- term index and retroactive interference scores. This suggests that the consumption of caffeine, at concentrations equivalent to those present in one large cup of coffee, prior to exercise, can impair an unhabituated individual's capacity to learn and recall auditory information in the short-term; and increases the likelihood for recently learned information to interfere with the recall of previously learned information. Even though these results need to be examined in a larger cohort, our findings are robust and consistent with other reports showing impaired performance on short term memory tasks following consumption of physiologically relevant concentrations of caffeine, particularly when demand levels of recall are high (Childs & de Wit, 2006; Klaassen et al., 2013; Loke, 1993).

While ours is the first known study in humans to investigate the acute influence of caffeine on postexercise memory, high doses of caffeine (30 mg/kg) administered 30 min prior to exercise 5 days per week for 4 weeks has been shown to suppress exercise-enhanced long-term and location memory in a murine model. Data suggested that this effect may be related to a decrease in hippocampal p-cAMP-response element binding protein (CREB) signaling (Cechella et al., 2014). Even though we did not observe a statistically significant detrimental effect of caffeine on indices of long-term postexercise recall, this is likely because the treatment protocol for this study involved a single dose of caffeine at a considerably lower concentration than that chronically administered by Cechella and colleagues (2014).

While speculative, this suggests that the irregular consumption of caffeine, equivalent to that in one cup of coffee, prior to exercise will not impede p-CREB signaling, or other mechanisms involved in the formation of long-term memories. Despite this, considering the literature as a whole, data

suggest that caffeine ingestion prior to exercise may reduce the potential learning and memory benefits others have found to be associated with exercise. However, reports on the effect of caffeine on memory are inconsistent. Indeed in contrast to our findings, some investigators

TABLE 3 Percent change from baseline in serum BDNF levels before, during and after exercise

	T20		T35		T65	
	Caffeinemean (SEM)	Placebo mean (SEM)	Caffeine mean (SEM)	Placebo mean (SEM)	Caffeine mean (SEM)	Placebo mean (SEM)
mBDNF (% change)	22.92* (6.02)	21.48 (5.73)	36.86* (7.35)	28.74** (4.47)	37.72* (6.18)	17.50 (6.79)
proBDNF (% change)	−1.14 (2.25)	0.19 (1.70)	2.21 (2.62)	0.81 (1.93)	0.62 (2.20)	2.56 (2.12)
mBDNF:proBDNF (% change)	23.70** (5.70)	21.55* (5.15)	35.25*** (7.44)	28.20** (4.22)	36.48*** (7.98)	15.27 (6.67)

Abbreviation: BDNF, brain-derived neurotrophic factor; SEM, standard error of the mean.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, $n = 6$.

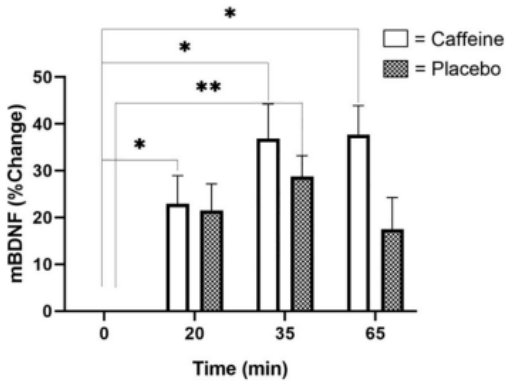

FIGURE 1 Percent change in mBDNF levels during (20 and 35 min) and post (65 min) exercise following the ingestion of 150 mg of caffeine or placebo. After the ingestion of 150 mg of caffeine total serum mBDNF levels were 22.92 ± 6.02%, 36.86 ± 7.35%, and 37.72 ± 6.18% higher at time 20, 35, and 65 min than at baseline. After the ingestion of the placebo total serum mBDNF levels were 28.74 ± 4.47% higher at time 35 min than at baseline. No significant percent change in proBDNF levels were found at any other time point. No significant difference was observed between treatment groups at any time point. Analyzed using repeated measures analysis of variance with Sidak's multiple comparisons post-hoc test ($F = 19.72$, $n = 6$). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

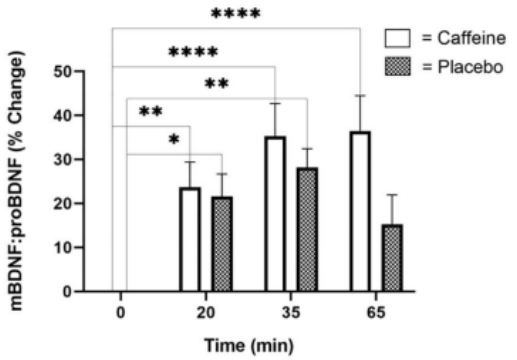

FIGURE 2 Percent change in the ratio of mBDNF:proBDNF during (20 and 35 min) and post (65 min) exercise following the ingestion of 150 mg of caffeine or placebo. After the ingestion of 150 mg of caffeine the ratio of mBDNF:proBDNF was 23.70 ± 5.70%, 35.25 ± 7.44%, and 36.48 ± 7.98% higher at time 20, 35, and 65 min than at baseline. After the ingestion of the placebo the ratio of mBDNF:proBDNF was 21.55 ± 5.15% higher at time 20 min and 28.20 ± 4.22% at time 35 min than at baseline. No significant percent change in the ratio of mBDNF:proBDNF was observed at time 65 min. No significant difference was observed between treatment groups at any time point. Analyzed using repeated measures ANOVA with Sidak's multiple comparisons post-hoc test ($F = 11.56$, $n = 6$). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

have observed caffeine ingestion to neither enhance nor impair memory (Amendola, Gabrieli, & Lieberman, 1998; Schmitt, Hogervorst, Vuurman, Jolles, & Riedel, 2003; Warburton, Bersellini, & Sweeney, 2001). For example Amendola et al. (1998) reported that while caffeine ingestion dose-dependently (64, 128, and 256 mg of caffeine) improved both mood and performance on a sustained- attention, reaction-timed task (Wilkinson Auditory Vigilance Test), no effects on working memory were detected. Contrary to our findings, others have reported that caffeine can improve some indices of memory. Notably, these studies either involved cognitively impaired participants or were conducted under conditions of either sleep deprivation, exhaustion or distraction (Alzoubi et al., 2013; Arendash et al., 2009; Beaumont et al., 2001; Hogervorst, Riedel, Schmitt, & Jolles, 1998; Sherman, Buckley, Baena, & Ryan, 2016). Under such conditions, some have argued that caffeine's positive effects onmemory are likely due to caffeine-induced increases in the performance of subservice, ancillary processes such as attention and reaction time (Borota et al., 2014; Brunyé, Mahoney, Lieberman, & Taylor, 2010; Kaplan et al., 1997; Riedel et al., 1995; Smith et al., 1999,

2005). This may explain the differential effects of caffeine on memory in studies involving participants with impaired, be it pathological or circumstantial, versus unimpaired cognition, such as those included in this study.

As reviewed by James and Rogers (2005), evidence from appropriately controlled studies suggests that the effects of caffeine on performance and mood (perceived to be net beneficial psychostimulant effects), may be attributable to the reversal of adverse withdrawal effects associated with short periods of abstinence. In light of this, future investigations into the effects of caffeine on memory should be designed to effectively control against confounding due to reversal of withdrawal effects. It is important to note that this was achieved in the current study by the unhabituation of participants to caffeine for at least 2 weeks prior to the experimental procedure. Consistent with the current uncertainty about the effect of caffeine on memory, caffeine's influence on the neurobiological and molecular mechanisms proposed to account for its behavioural effects is likewise varied and highly dependent on experimental conditions. Although an in-depth discussion is beyond the scope of this article, relevant to our findings, caffeine induced reductions in postexercise memory performance in rats has been associated with decreased hippocampal p-CREB activation and signaling (Cechella et al., 2014). Importantly CREB, a cellular transcription factor, affects memory consolidation in part through its promotion of increased mBDNF expression (Kim et al., 2012; Yoo, Lee, Sok, Ma, & Kim, 2017).

Thus, mBDNF expression is reduced if CREB activation is impaired. What's more, A2A receptor knock out mice have been shown to have reduced hippocampal BDNF levels compared with wild type mice (Potenza et al., 2007). Thus, it can be theorized that caffeine may adversely affect memory, at least in part, through A2A receptor/CREB/BDNF dependent mechanisms. While we did not observe a significant difference in BDNF levels between caffeine and placebo treatments in this study, this is likely related to exercise induced thrombocytosis. Approximately 99% of blood BDNF is bound to platelets (Radka, Holst, Fritsche, & Altar, 1996). During exercise splenic constriction (Walsh & Tschakovsky, 2018) results in a substantial rise in blood platelets (Anz et al., 2019; Walsh & Tschakovsky, 2018). Importantly platelet bound BDNF is not a static pool, as BDNF can be released under shearing stress, such as present in active muscles (Fujimura et al., 2002; Walsh, Bentley, Gurd, & Tschakovsky, 2017; Walsh & Tschakovsky, 2018).

This likely accounts for the time dependent increase in blood/serum BDNF levels observed in both treatment groups in response to exercise. The significance of this rise would also mask any smaller change in BDNF due to inhibition of systemic A2A receptors by caffeine ingestion. This could therefore account for the lack of significant difference in the mBDNF:proBDNF ratio between treatment groups at any time point. Though systemic BDNF has been shown to cross the blood brain barrier, cerebrospinal fluid was not collected in this study and therefore changes in brain/central BDNF levels due to either exercise or caffeine treatments were unable to be assessed. Consequently, though our results showed a clear effect of caffeine on short-term memory and learning indices postexercise, we were not able to confirm that this was mediated through reduced brain BDNF concentrations.

While the possible effect of caffeine on A2A receptors and mBDNF remain a plausible explanation for our observations alternative (or complementary) explanations may also include caffeine's well-known vasoconstrictive effects (Diukova et al., 2012). This was postulated to explain why, using near-infrared spectroscopy, cerebral oxygenated hemoglobin levels were found to be significantly reduced during a working memory paradigm (visual 2-back) after caffeine (200 mg) administration (Heilbronner, Hinrichs, Heinze, & Zaehle, 2015). Relevantly caffeine induced vasoconstriction has been shown to decrease cerebral perfusion (Cameron, Modell, & Hariharan, 1990; Laurienti et al.,

2003) which has been independently associated with reduced performance on immediate verbal memory tasks (Alosco et al., 2013).

Although the results generated by this study are sound, several limitations are present. In addition to the possibility that exercise induced thrombocyte release masked potential changes in brain/central mBDNF that may have occurred in response to caffeine (discussed above), it is likely that the small sample size hindered our capacity to detect potentially significant changes on other memory indices postexercise. The small sample size also reduces the generalizability of results to the wider population and extrapolation should be done with caution. Further as the RAVLT test was always administered postexercise the effects of caffeine alone on memory cannot be determined. Accordingly results presented should always be considered in relation to postexercise memory only. Finally, participants were also intentionally unhabituated to caffeine. While necessary to control for withdrawal, whether caffeine would have the same negative effect on post exercise learning and short term recall in regular caffeine users remains to be established.

CONCLUSION

In conclusion we have shown for the first time that caffeine ingestion prior to exercise impairs unhabituated individual's postexercise short-term capacity to learn and recall auditory information. However, it is yet to be elucidated whether this is through caffeine's modulating effects on BDNF. Considering the widespread promotion of exercise to improve cognitive function by health professionals and the equally widespread use of caffeine during exercise, individuals should be made aware of these potential detrimental effects.

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