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Can caffeine intake combined with aerobic exercise lead to improvement in attentional and psychomotor performance in trained individuals?

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ABSTRACT

To evaluate the acute effects of ingestion of 500 mg of caffeine in addition to aerobic exercise on the optimization of cognitive attention tasks and simple reaction time. Twenty men were randomly divided into two groups, caffeine (CAF) and placebo (PLA), and underwent cardiopulmonary exercise testing and cognitive testing (D2SLK, D2GZ, D2F% and TRS). Then, both ingested 500 mg of caffeine or placebo (double blind), and after 60 min performed a 30-minute continuous exercise session at 70 % VO2Max. Cognitive tests were repeated immediately after exercise, and after 30 min. D2SLK, D2GZ, D2F% and TRS scores were compared by repeated measures ANOVA. The magnitude of the effect was established, and it was considered meaningful $p = 0.05$. CAF is able to alter D2SLK and also reduce D2F% (0.001 - moderate effect, 0.82) and improve the task after 30 min of exercise ($p = 0.014$ - moderate effect 0.95). The TRS showed significant gains for the CAF group compared to PLA (0.000 - high effect 1.76). Caffeine induces significant effects in attention and reaction time domains independent of the effect of aerobic exercise.

1. Background

Caffeine is a trimethylxanthine commonly consumed by the population (Fredholm and Battig, 1999; Kruk and Chmura, 2001; Brunye and Mahoney, 2010a, b; Duncan and Oxford, 2011), and its daily intake in moderate doses has psychostimulant properties and is capable of producing positive and significant effects on attention and reaction time (Fredholm and Battig, 1999; Kruk and Chmura, 2001; Brunye and Mahoney, 2010a, b; Duncan and Oxford, 2011) from approximately 30 min after ingestion and complete absorption through the gastrointestinal tract (Durlac and Edmunds, 2002).

Caffeine effects could be related to the release of serotonin in the cerebral cortex and/or the interaction of methylxanthine with adenosine receptors in the brain (Ribeiro and Sebastiao, 2010), producing inhibitory action of the enzymes adenylcyclase and phosphodiesterase, increasing the concentration of an important physiological signalled, the monophosphate adenosine (Cyclic AMP) (Fredholm, 1985). Thus, substances such as catecholamines are released inducing chronotropism and positive inotropism (Benowitz, 1990), producing a state of preparedness, and alertness, which may favour cognitive tasks that require attention (Smith and Christopher, 2013) and rapid motor response (Fredholm, 1985; Fisone and Borgkvist, 2004). Caffeine intake recommendation varies by gender and age (Temple and Bernard, 2017).

The facilitative effects of caffeine intake seem to be equally induced by performing one or more aerobic exercise sessions, generally manifesting itself as dependent on the intensity or volume of the training, thus being of an optimal exercise magnitude (Kamijo and Nishihira, 2004, 2007). Smith et al. (Smith and Blumenthal, 2010) observed a

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moderate effect of exercise on attentional performance and processing speed, with less significant results when it comes to psychomotor performance. Similar to the study by Smith et al. (Smith and Blumenthal, 2010) and Chang et al. (Chang and Labban, 2012) demonstrated a positive effect of exercise influence on attention and psychomotor performance. From this perspective, then, there seems to be an appropriate effect on the “neurotransmitter-receptor” or “substance-receptor” interaction via caffeine administration or through exercise, which enhances cognitive and psychomotor processes (Smith, 2002).

More specifically on the topic in question, Hogervorst et al. (Hogervorst et al., 2008) conducted in three groups of trained individuals a supplementation with bar containing 45 g carbohydrate and 100 mg caffeine (CAF), caffeine-free isocaloric bar (CHO) or 300 ml placebo drink (BP) before performing 2 h and 30 min of aerobic exercise. They were evaluated for cognitive function (Stroop and T2EX quick visual information processing tests) preexercise, during and 5 min after exercise. The results showed that the use of CAF provided a higher T2EX compared to the use of CHO and BP, and there were no differences in physiological parameters between the conditions (CAF vs CHO vs BP). Regarding the Stroop test, the reaction speed was higher with the use of CAF when compared to CHO and BP, during exercise (70 and 140 min) and after exercise (180 min). In all parameters of the visual information processing tests (reaction time, accuracy and error rate and error rate), performance was better with CAF consumption along with aerobic exercise compared to other conditions (CHO and BP). This improvement is most seen in complex cognitive tests over tests that use simple motor reaction time, suggesting that caffeine appears to mediate central improvements.

However, High levels of anxiety, irritability, stress, reduced cognitive performance, and other deleterious manifestations are observed when central nervous system excitation exceeds physiological limits (Brice and Smith, 2002; Temple and Bernard, 2017), and this may occur with the absence of optimal training magnitude and also inadequate caffeine intake. Thus, despite this preliminary understanding, it is not clear what the impact of different intensities, or volume, as well as different caffeine dosages would have on cognitive and psychomotor processes, fitting investigation.

Therefore, the purpose of the present study was to assess whether 500 mg caffeine intake would cause additional effects in a single moderate aerobic training session and then whether the combination of these strategies would be able to improve cognitive and psychomotor processes by promoting greater facilitatory effects than attention and time to simple motor reaction. We believe that caffeine will provide additional effects to aerobic exercise, which in turn will enhance attention and psychomotor performance immediately after exercise.

The present study used the assumptions described by the International Committee of Medical Journal Editors (ICMJE) as a reference and respected all the items proposed in the guidelines "CONSORT for reporting parallel group randomized trials (Schulz and Altman, 2010). All procedures were performed in accordance with the Declaration of Helsinki and included in the clinical trial registration of the US National Institutes of Health (ClinicalTrials.gov; NCT02511964).

2. Methods

2.1. Subjects

Twenty physically active, non-smoking, right-handed men were invited to participate in the study through advertisements at the university where the study was conducted between 2014 and 2015. All responded to Edinburgh Handedness Inventory or laterality (Oldfield, 1971; Brito and Brito, 1989) as well as reported regular use of caffeine consumption through survey. All subjects were regular tea and/or coffee drinkers, and the consumption of 200 mg/day of caffeine for moderate drinkers was used as a exclusion criteria (Brice and Smith, 2002). Subjects who ingested more than 400 mg of caffeine/day, who had mental or physical diseases, or who used psychoactive or ergogenic substances were excluded.

Table 1
Sample Characteristics.

Characteristics	Group CAF (mean ± standard deviation)	Group PLA
Age (years)	28.3 ± 5.9	30.9 ± 7.2
Body mass (kg)	73.5 ± 6.2	78.3 ± 8.3
Height (cm)	175.7 ± 5.9	178.2 ± 7.2
Percent fat (%)	17 ± 4.2	13 ± 4.4

Note: Sample characteristic data presented mean ± standard deviation, $p > 0.05$.

Before participating in the study, all participants were informed about the procedures, had their questions answered, and signed a consent form. All subjects performed a risk stratification questionnaire for coronary artery disease, and were classified as low risk. Table 1 describes the sample characteristics.

Using the G-Power (Free Version 3.0.5) statistical package for “ANOVA Repeated Measures Between Factors” analysis with three measurements in two groups, the sample size considered an error of 5 %, a statistical power of 80 % and a size effect of 0.60 (moderate), resulting in 20 participants. The study was approved by the Ethics Committee of the University of Salgado de Oliveira (UNIVERSO), number (# 1,220,352).

2.2. Experimental procedures

The experimental procedures were divided into two visits. In the first visit, three stages were performed: a) signature of the consent and inclusion term; b) anthropometric measurements and risk stratification for coronary artery disease (CAD) as suggested by ACSM (2010); c) cardiopulmonary exercise test. At the second visit, the subjects initially performed the first measure of cognitive attention and reaction time tests, and were randomly divided into two groups: a) who would use caffeine (CAF); b) or placebo (PLA), both in a blinded experiment. All ingested 500 mg of caffeine and/or placebo, and rested for 60 min to perform the cognitive and psychomotor tests again. Subsequently, subjects performed a continuous aerobic exercise session on a 70 % VO_{2Max} treadmill for 30 min, and immediately after 30 min, new cognitive and psychomotor test batteries were performed. The experimental approach is shown in Fig. 1.

2.3. Anthropometry

It was used standard assessment established by the International Society for the Advancement of Kinanthropometry (ISAK) to determine the following anthropometric measures: body weight and height (Mechanic, Filizola, Brazil), and skinfold (Slim Guide, Rosscraft, Canada). We estimated the body fat percentage through Jackson & Pollock’s equation (Jackson and Pollock, 1978).

2.4. Cardiopulmonary stress test

The subjects started walking on the treadmill at 5.0 km/h 1 and 1% of inclination for a period of 3 min. From this initial stage, 1.0 km/h 1 (approx. 1 MET) was added until voluntary exhaustion. Oxygen consumption was measured using the VO_{2000} ergospirometric Respiratory Exchange Analysis Equipment (CPX-D Medical Graphics TM, Saint Paul, MN, USA) with the calibration according to the manufacturer's specifications. The heart rate (HR) responses (Polar Monitor® model RS800), as well as the subjective perceived exertion (RPE) (adapted scale of Borg 0–10), were monitored and recorded every minute until the moment of exhaustion. The presence of signs or symptoms mentioned, or the maximal voluntary exhaustion itself was used with criteria for the

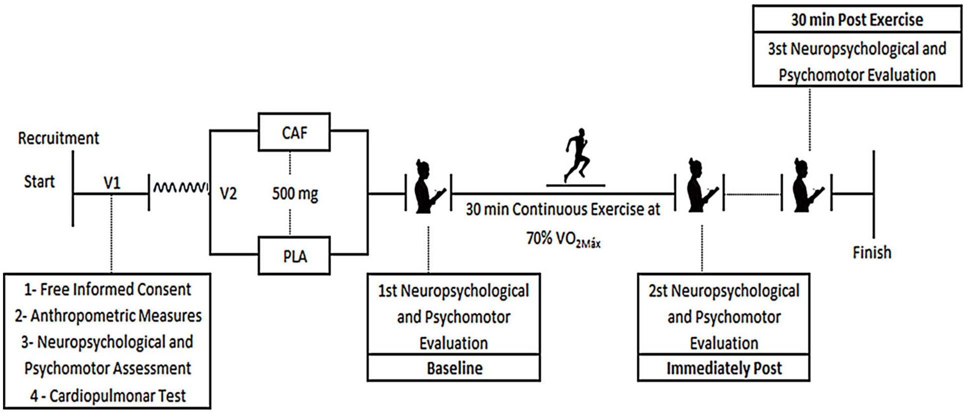

Fig. 1. Experimental approach.

completion of the test.

2.5. Neurocognitive assessment

The neurocognitive evaluation was performed using the D2 test to analyse the domains of attention, and the psychomotor test of simple reaction time (SRT).

The D2 test consisted of paper sheets with 14 lines with 47 mixed letters randomly in D or P for evaluation of sustained and selective attention. The subjects were instructed to mark in a period of 20 s on each line, and within a sequence of letters ("D" and "P"), only the letter ”d” with two strokes, which can be both up, down or up and down. After 20 s an acoustic signal was emitted for the subjects to be directed to the next line. The total number of symbols worked within the D2 test (i.e., GZ – Quantitative measurement of the working speed), the number of correct answers and fewer confusion errors (i.e., SKL – A measure that reflects the time of attention), and the total number of errors (F%; Confusion and elimination errors) related to GZ were calculated and parameterized for sustained and selective attention. A value of 100 represents poor performance.

The TRS was evaluated after a learning session using computer software based on the MATLAB platform. The software provided random simple light stimuli that lasted a total of one minute and produced 10 stimuli. Subjects were instructed to press a certain key on a computer keyboard with their right index finger whenever a light stimulus appeared. The system calculated the SRT for all stimuli, generating scores.

2.6. Exercise protocol

The subjects were positioned on the treadmill after a 5 min free warm-up period and started the continuous exercise protocol with intensity adjusted to 70 % of VO$_{2Max}$. Both groups (CAF and PLA) were encouraged to stay active for 30 min. The subjects could leave the exercise during the procedure at the sign of any complications or due to fatigue. At the end of the exercise, a brief 3 min slow speed walk was performed. HR and SPE were recorded every five minutes during exercise. All tests were performed at the same day time and with controlled temperature between 21 and 23°.

2.7. Statistical analysis

A descriptive analysis of the data was previously performed, and the data was described as mean ± standard deviation (SD). After Shapiro-Wilk test of normality ($p =$ 0.803 - assumed normality), and heteroscedasticity assumptions, Two way ANOVA was performed to compare the treatment (CAF vs PLA) given the dependent variables (scores D2 and SRT). Delta% (Δ%) as well as effect size magnitude (ESM) were also determined and qualified according to Cohen's “d” index. All analyses will be performed using SPSS 20.0 for Windows® software (Chicago, USA) with a statistical significance of $p \geq 0.05$.

3. Results

Regarding the kinanthropometric data there were no significant differences between the groups (Table 1). We observed through the analysis of the indicators of the attention and psychomotor response test (D2 test) (Fig. 2) the best response in the D2-F% (Fig. 2A), D2-GZ (Fig. 2B) and D2-SKL scores (Fig. 2C) with CAF intake when compared to PLA.

There was a significant interaction between time and group in the D2-GZ score (F (1.34, 24.2) = 20.742; $p < 0.001$), D2-SKL (F (2.36) = 10.556; $p < 0.001$) D2-F% (F (2.36) = 10.509; $p < 0.001$). There were also significant effects for time on the three indicators (F (1.34, 24.2) = 25.559; $p < 0.001$; F (2.36) = 11.481, $p < 0.001$; (F (2.36) = 5.926; $p < 0.001$) and the main significant effect for the group was found only in the D2-GZ score (F (1.18) = 6.382; $p = 0.021$), other scores D2-SKL and D2-F% (F (1.18) = 3.241, $p = 0.089$; F (1.18) = 0.047; $p = 0.831$, respectively).

Post-hoc analysis revealed no significant differences between the baseline and post-CAF/PLA intake groups in any of the scores D2-GZ, D2-SKL, or D2-F% ($p > 0.05$), however, differences were found between post-exercise groups in all scores, D2-GZ ($p < 0.001$), D2-SKL ($p = 0.001$) and D2-F% ($p = 0.\ 010$) with CAF participants performing better on all three measures. There were also significant differences in the CAF group in the D2-GZ, D2-SKL and D2-F% scores when comparing exercise time with baseline ($p < 0.001$; $p < 0.001$; $p = 0.001$, respectively) and caffeine consumption ($p < 0.001$; $p < 0.001$; $p = 0.002$, respectively), with participants performing better after exercise on the three indicators. There were no significant changes in the PLA group over time in any of the D2 test indicators.

Through the simple reaction time test (SRT) we also observed a better response with a reduction in the SRT post exercise and also after ingestion in the CAF group when compared to PLA (Fig. 3). There was a significant interaction between time and group (F (1.23.26) = 6.606; $p = 0.004$). There were significant major effects for time (F (1.23.26) = 20.981; $p < 0.001$) and for the group (F (1.18) = 16.264; $p = 0.001$).

Post-hoc analysis revealed no significant differences between the groups at baseline ($p = 0.552$), but there were already differences between the groups after CAF/PLA intake ($p = 0.029$) and also after exercise ($p < 0.001$). Therefore, we observed that in the CAF group, the SRT decreased over time, as there were significant differences when comparing baseline performance and caffeine intake ($p = 0.014$), as well as post caffeine consumption and post exercise ($p < 0.001$), which did not occur in the PLA group, which did not change

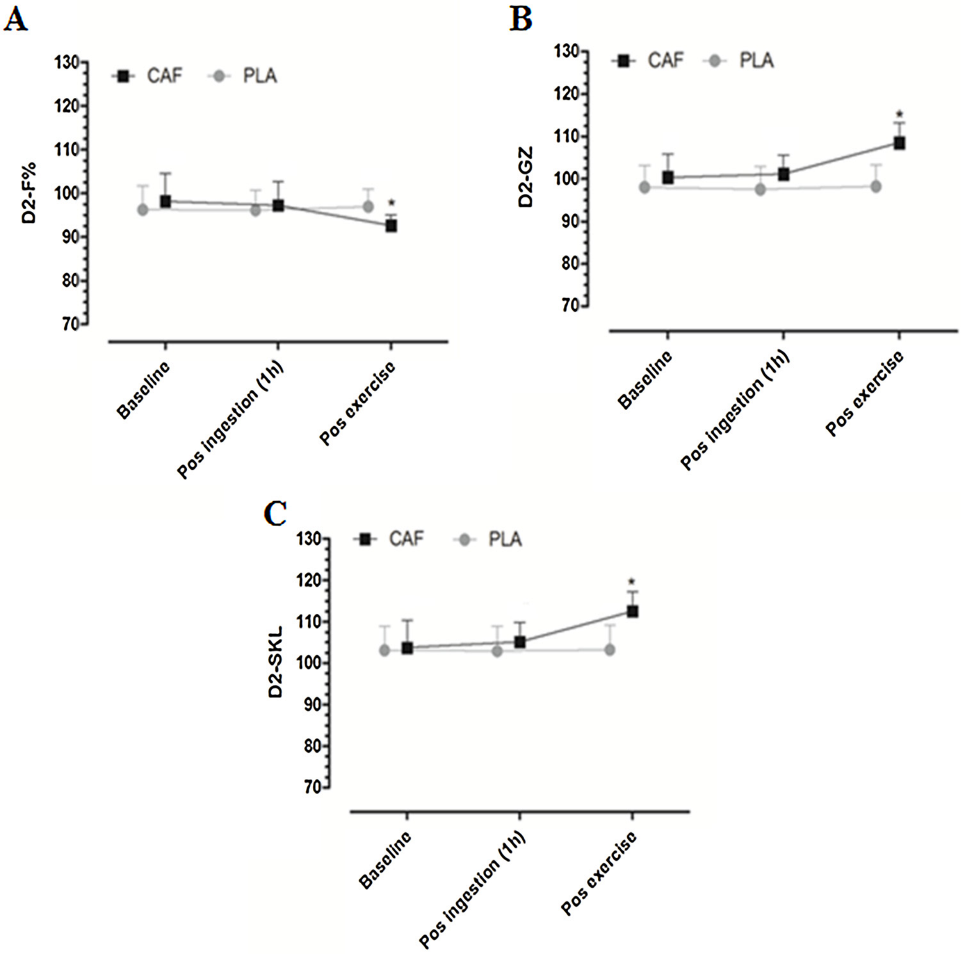

Fig. 2. Results of D2 performance over time for participants with caffeine intake plus aerobic exercise (CAF group) and participants with placebo plus aerobic exercise (PLA group). A. The total number of confusion and elimination errors (D2-F%;). B. Quantitative measurement of working speed (D2-GZ) C. Measurement that reflects the attention span the number of correct answers minus confusion errors (D2-SKL). Values are expressed as mean ± SD (n = 20) for groups ingesting 500 mg of caffeine (CAF) or 500 mg of placebo (PLA) P ≤ 0.05 * CAF vs PLA.

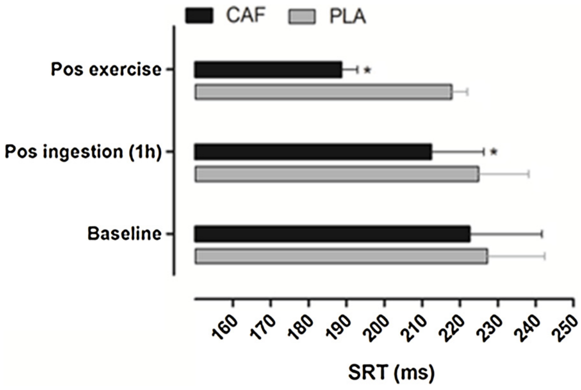

Fig. 3. SRT performance results over time. Values are expressed as mean ± SD (n = 20) for groups that ingested 500 mg of caffeine (CAF) or 500 mg of placebo (PLA) P ≤ 0.05; * CAF vs PLA.

significantly over time.

The effect size analysis for each outcome measure as well as the group averages at each time point is shown in Table 2.

In the CAF group, significant effects were found between baseline and post-exercise evaluations on all reported outcomes (d = 0.82, a = 1.76). The smallest effect was reported on the D2-F% score, while the largest was on the SRT performance. Within the PLA group there were no significant effects, although no significant effects were found on SRT performance.

Table 2
Standardized mean and SD for the caffeine and placebo group at baseline, after caffeine/placebo intake and after exercise.

Test	CAF group				PLA group			d
	Baseline	AC	AE	d	Baseline	AC	AE	
D2-SKL	103.7 (6.6)	105.1 (4.6)	112.5 (4.7)	1.33	103.1 (5.8)	102.9 (5.9)	103.2 (5.9)	0.01
D2-GZ	100.3 (5.5)	101.1 (4.5)	108.5 (4.6)	1.49	98.0 (5.1)	97.5 (5.4)	98.2 (5.2)	0.04
D2-F%	98.1 (6.4)	97.2 (5.4)	92.6 (2.5)	0.86	96.2 (5.5)	96.1 (4.5)	96.9 (4.0)	0.13
SRT	222.5 (19.2)	212.3 (14.0)	188.6 (4.3)	1.76	227.2 (15.2)	224.9 (9.3)	217.8 (4.1)	0.32

***Note*:** CAF: caffeine group; PLA: placebo group; AC: 1 h after caffeine or placebo intake; AE: after aerobic exercise.

4. Discussion

In our study we sought to extract possible additional effects of caffeine intake combined with aerobic exercise on the improvement of attentional and psychomotor cognitive processes. Responses regarding attentional processes D2SKL, D2GZ, D2F% were presented only late at the end of the running session, while for the SRT, 60 min. After caffeine ingestion, significant supplementation results were already observed, suggesting distinct interaction mechanisms regarding attention and SRT, possibly central and/or peripheral. Moreover, the magnitude of the effect size ranged from moderate to high (d = 0.86–1.76), which gives an important clinical significance to our results, since in a healthy elderly population technically more susceptible to changes from this interventional nature, the effects of exercise presented to the domains of attention and processing speed were only moderate (Hedges index "g" = 0.158 ± 0.52 – p = 0.03) (Smith and Blumenthal, 2010).

According to Winwood (Winwood and Pritchard, 2019), caffeine is one of the most used supplements for preparation on competition days and it can improve sports performance through the evolution of cognitive and psychological elements. However, the effects of aerobic exercise on attention improvement or SRT are still controversial, as well as for other cognitive domains (Nurminen and Niittynen, 1999; Smit and Rogers, 2000). Positive effects on cognition may be influenced by age, previous cognitive impairment, level of training, or the different assessment methods employed, such as complex or less complex tests (Smith and Blumenthal, 2010; Temple and Bernard, 2017).

In our study, we observed that the participants profile may have directly interfered with obtaining only minor advances in the D2 attention tests, including the sum of the strategies. Surprisingly, the CAF group exhibited high scores and magnitude of effect for attention task, but only after exercise (D2SKL - 103.7 ± 6.6 > 112.5 ± 4.7; D2GZ - 100.3 ± 5.5 > 108.5 ± 4.6; D2F% - 98.1 ± 6.4 > 92.6 ± 2.5). In this sense, we know that caffeine intake is dose-dependent (Kaplan and Greenblatt, 1997), and at low doses of approximately 100 mg, there appears to be no significant effect on cognition (Brunye and Mahoney, 2010a, b), which does not replicate at high caffeine doses (Kaplan and Greenblatt, 1997; Temple and Bernard, 2017), which was not observed in our study. Hogervorst et al. (Hogervorst and Riedel, 1999) for example, applied five distinct drinking conditions: 1) water; 2) carbohydrate and electrolyte solutions (CES) in the placebo condition (68.8 g/l); 3) CES containing low doses of caffeine (150 mg/l), 4) medium doses (225 mg/l) and 5) high doses of caffeine (320 mg/l) in triathlete cyclists who exercised on an exercise bike in 1 h time trial. Cognitive and psychomotor assessments were performed before and immediately after the time trial. Before exercise 8 ml/kg of the drink was consumed and during exercise 6 ml/kg. The results showed that caffeine consumption (150, 225 and 320 mg/l) provided improvements in the post-exercise selective attention test "Stroop test" compared to the condition of water consumption. However, only caffeine intake of 225 mg/l was beneficial for greater efficiency in the Signal Detection Task - a post-exercise shifting of attention strategy compared to water consumption.

Comparing this scenario with the design of our study, Hogervorst et al. (Hogervorst and Riedel, 1999) and other studies (Pomportes and Brisswalter, 2017) applied caffeine during exercise, low and medium caffeine dosages were the ones that most affected cognitive functions after exercise. The effect of exercise on the improvement of cognitive functions seems to occur as a result of the increased central activation due to the provided physiological stress (Hogervorst and Riedel, 1999). The use of caffeine would then act as a perceived fatigue suppressor, thus providing a better performance on cognitive tests (Hogervorst and Riedel, 1999; Pomportes and Brisswalter, 2017).

It is noteworthy that regarding attention domain, caffeine action is mediated through central blockade of adenosine agonist receptors, mainly A1 and A2A (higher affinity), inhibiting the formation of AMPc and phosphodiesterase enzyme, with sympathetic nervous system stimulation, and excitatory and attention increase (Lieberman, 2003; Fisone and Borgkvist, 2004). However, we did not observe this effect within the first hour of intervention, and this may be associated with physiological changes linked to a delay in central responses compared to peripheral interactions. We speculate that aerobic exercise may have specifically acted on increasing the permeability of the blood-brain barrier (BBB), favoring the effects of caffeine interaction on the brain (Malkiewicz and Szarmach, 2019). Evidence suggests that after prolonged exercise, due to temperature rise, activity of catecholamines and indolamines increase, mainly mediated via $5HT_2$ receptors (Sharma and Cervos-Navarro, 1991), as well as inflammatory mediators, the permeability of the BBB changes (Chen and Ghribi, 2010). Moreover, depending on physical fitness, the training routine could provoke angiogenesis via endothelial vascular growth factors (VEGF) (Kraus and Stallings, 2004), thus changing the permeability coefficient and surface area (Bradbury, 1993). Caffeine is a relevant substance for controlling the integrity of BBB (Chen and Ghribi, 2010). It may confer a defensive effect against mental disorders, limit the entry of pathogens, inflammatory processes, and act indirectly on improving cognition (Chen and Ghribi, 2010).

Different investigations have shown that acute aerobic exercise in moderate intensity reduces the SRT (Tomporowski and Tinsley, 1996; Chmura and Krysztofiak, 1998; Kruk and Chmura, 2001; Kamijo and Nishihira, 2004). However, this response seems to differ according to the complexity of the task performed, such as when performing a dual task paradigm (Brisswalter and Arcelin, 1997). In singular tasks the magnitude of this response as shown by Chang et al. (Chang and Labban, 2012) exhibits only little influence of exercise on psychomotor performance (choice reaction time and simple reaction time). In our study the magnitude of SRT change was increased after 60 min from caffeine intake, as well as had its SRT values further reduced soon after exercise, suggesting additional effects of caffeine on exercise.

Unlike the attention domain, caffeine may seem to act facilitating motor action, both by central and peripheral interaction. For example, caffeine is structurally similar to adenosine, and thus competing antagonistically by blocking adenosine receptors (A1 and A2), favoring brain motor performance (Nehlig and Daval, 1992). In addition, as a psychoactive substance, it seems to alter the activation activity of the ascending reticular system, increasing excitatory levels and leading to cortical activity increase (Nehlig and Daval, 1992; Lorist and Tops, 2003).

Peripherally, caffeine is known to act by increasing the firing frequency of cholinergic neurons (antagonically inhibited by interaction with adenosine molecules), releasing a higher concentration of acetylcholine in the neuromuscular junction, and increasing calcium influx (Ca^{+2}). by the sarcoplasmic reticulum. The mechanism seems to be related to channel activation of Ca^{+2} induced by Ca^{+2} release (Carter and O'Connor, 1995). Ryanodine receptors such as RYR2 mediate the Ca^{+2} release-induced Ca^{+2} mechanism and increase its sensitivity in the presence of caffeine (Carter and O'Connor, 1995). This may be associated with the quick motor response observed before the onset of exercise and increased after exercise.

Among the limitations of the present study, we can mention the lack of a no training group, the training duration (i.e., just 22 min effectively), the level of cardiorespiratory conditioning (i.e., physically active) and the gender (by not including females) of the sample, since we know that these factors can directly interfere with cognitive responses to exercise and caffeine use.

5. Conclusion

Caffeine was able to induce significant additional effects to aerobic exercise, improving attention span and reaction time. Considering the exercise performed, the caffeine dosage applied and the research subjects, it is suggested that further research be carried out in order to better understand the interrelationship between the different types of exercise and caffeine doses and their combination on the cognitive domains and also elucidate the beneficial and harmful effects of this combination on attentional domains and reaction time in order to contribute to safer exercise prescription strategies in healthy populations and also to sports performance.

Conflict of interest

The authors declare no conflict of interest.

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CRediT authorship contribution statement

Sergio Machado: Conceptualization, Methodology, Project administration, Supervision, Writing - original draft, Writing - review & editing. **Alberto Souza Sá Filho:** Formal analysis, Writing - review & editing. **Carlos Campos:** Formal analysis, Writing - review & editing. **Carolina Cavalcante de Paula:** Writing - review & editing. **Fabyana Bernardes:** Formal analysis, Writing - review & editing. **Eric Murillo-Rodriguez:** Formal analysis. **Geraldo A. Maranhão Neto:** Formal analysis, Writing - original draft. **Eduardo Lattari:** Conceptualization, Methodology, Project administration.

References

ACSM, 2010. ACSM´S Guidelines for Exercise Testing and Prescription. Lippincott Williams and Wilkins, Baltimore.

Benowitz, N.L., 1990. Clinical pharmacology of caffeine. Annu. Rev. Med. 41, 277–288. https://doi.org/10.1146/annurev.me.41.020190.001425.

Bradbury, M.W., 1993. The blood-brain barrier. Exp. Physiol. 78 (4), 453–472.

Brice, C.F., Smith, A.P., 2002. Effects of caffeine on mood and performance: a study of realistic consumption. Psychopharmacology (Berl.) 164 (2), 188–192. https://doi.org/10.1007/s00213-002-1175-2.

Brisswalter, J., Arcelin, R., et al., 1997. Influence of physical exercise on simple reaction time: effect of physical fitness. Percept. Mot. Skills 85 (3 Pt 1), 1019–1027. https://doi.org/10.2466/pms.1997.85.3.1019.

Brito, G.N., Brito, L.S., et al., 1989. Lateral preferences in Brazilian adults: an analysis with the Edinburgh Inventory. Cortex 25 (3), 403–415. https://doi.org/10.1016/s0010-9452(89)80054-1.

Brunye, T.T., Mahoney, C.R., et al., 2010a. Acute caffeine consumption enhances the executive control of visual attention in habitual consumers. Brain Cogn. 74 (3), 186–192. https://doi.org/10.1016/j.bandc.2010.07.006.

Brunye, T.T., Mahoney, C.R., et al., 2010b. Caffeine modulates attention network function. Brain Cogn. 72 (2), 181–188. https://doi.org/10.1016/j.bandc.2009.07.013.

Carter, A.J., O'Connor, W.T., et al., 1995. Caffeine enhances acetylcholine release in the hippocampus in vivo by a selective interaction with adenosine A1 receptors. J. Pharmacol. Exp. Ther. 273 (2), 637–642.

Chang, Y.K., Labban, J.D., et al., 2012. The effects of acute exercise on cognitive performance: a meta-analysis. Brain Res. 1453, 87–101. https://doi.org/10.1016/j.brainres.2012.02.068.

Chen, X., Ghribi, O., et al., 2010. Caffeine protects against disruptions of the blood-brain barrier in animal models of Alzheimer's and Parkinson's diseases. J. Alzheimers Dis. 20 (Suppl. 1), S127–141. https://doi.org/10.3233/JAD-2010-1376.

Chmura, J., Krysztofiak, H., et al., 1998. Psychomotor performance during prolonged exercise above and below the blood lactate threshold. Eur. J. Appl. Physiol. Occup. Physiol. 77 (1–2), 77–80.

Duncan, M.J., Oxford, S.W., 2011. The effect of caffeine ingestion on mood state and bench press performance to failure. J. Strength Cond. Res. 25 (1), 178–185. https://doi.org/10.1519/JSC.0b013e318201bddb.

Durlac, P.J., Edmunds, R., et al., 2002. A rapid effect of caffeinated beverages on two choice reaction time tasks. Nutr. Neurosci. 5 (6), 433–442. https://doi.org/10.1080/1028415021000039211.

Fisone, G., Borgkvist, A., et al., 2004. Caffeine as a psychomotor stimulant: mechanism of action. Cell. Mol. Life Sci. 61 (7–8), 857–872. https://doi.org/10.1007/s00018-003-3269-3.

Fredholm, B.B., 1985. On the mechanism of action of theophylline and caffeine. Acta Med. Scand. 217 (2), 149–153.

Fredholm, B.B., Battig, K., et al., 1999. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. Pharmacol. Rev. 51 (1), 83–133.

Hogervorst, E., Riedel, W.J., et al., 1999. Caffeine improves cognitive performance after strenuous physical exercise. Int. J. Sports Med. 20 (6), 354–361. https://doi.org/10.1055/s-2007-971144.

Hogervorst, E.E.F., Bandelow, S., Schmitt, J., et al., 2008. Caffeine improves physical and cognitive performance during exhaustive exercise. Med. Sci. Sport Exerc. 40 (10), 1841–1851.

Jackson, A., Pollock, M., 1978. Generalized equations for predicting body density of men. Br. J. Nutr. 40, 497–504.

Kamijo, K., Nishihira, Y., et al., 2004. Changes in arousal level by differential exercise intensity. Clin. Neurophysiol. 115 (12), 2693–2698. https://doi.org/10.1016/j.clinph.2004.06.016.

Kamijo, K., Nishihira, Y., et al., 2007. The interactive effect of exercise intensity and task difficulty on human cognitive processing. Int. J. Psychophysiol. 65 (2), 114–121. https://doi.org/10.1016/j.ijpsycho.2007.04.001.

Kaplan, G.B., Greenblatt, D.J., et al., 1997. Dose-dependent pharmacokinetics and psychomotor effects of caffeine in humans. J. Clin. Pharmacol. 37 (8), 693–703. https://doi.org/10.1002/j.1552-4604.1997.tb04356.x.

Kraus, R.M., Stallings 3rd, H.W., et al., 2004. Circulating plasma VEGF response to exercise in sedentary and endurance-trained men. J. Appl. Physiol. 96 (4), 1445–1450. https://doi.org/10.1152/japplphysiol.01031.2003. 1985.

Kruk, B., Chmura, J., et al., 2001. Influence of caffeine, cold and exercise on multiple choice reaction time. Psychopharmacology (Berl.) 157 (2), 197–201.

Lieberman, H.R., 2003. Nutrition, brain function and cognitive performance. Appetite 40 (3), 245–254.

Lorist, M.M., Tops, M., 2003. Caffeine, fatigue, and cognition. Brain Cogn. 53 (1), 82–94.

Malkiewicz, M.A., Szarmach, A., et al., 2019. Blood-brain barrier permeability and physical exercise. J. Neuroinflammation 16 (1), 15. https://doi.org/10.1186/s12974-019-1403-x.

Nehlig, A., Daval, J.L., et al., 1992. Caffeine and the central nervous system: mechanisms of action, biochemical, metabolic and psychostimulant effects. Brain Res. Brain Res. Rev. 17 (2), 139–170.

Nurminen, M.L., Niittynen, L., et al., 1999. Coffee, caffeine and blood pressure: a critical review. Eur. J. Clin. Nutr. 53 (11), 831–839.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9 (1), 97–113. https://doi.org/10.1016/0028-3932(71)90067-4.

Pomportes, L., Brisswalter, J., et al., 2017. Cognitive performance enhancement induced by caffeine, carbohydrate and guarana mouth rinsing during submaximal exercise. Nutrients 9 (6). https://doi.org/10.3390/nu9060589.

Ribeiro, J.A., Sebastiao, A.M., 2010. Caffeine and adenosine. J. Alzheimers Dis. 20 (Suppl. 1), S3–15. https://doi.org/10.3233/JAD-2010-1379.

Schulz, K.F., Altman, D.G., et al., 2010. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. Trials 11, 32. https://doi.org/10.1186/1745-6215-11-32.

Sharma, H.S., Cervos-Navarro, J., et al., 1991. Increased blood-brain barrier permeability following acute short-term swimming exercise in conscious normotensive young rats. Neurosci. Res. 10 (3), 211–221. https://doi.org/10.1016/0168-0102(91)90058-7.

Smit, H.J., Rogers, P.J., 2000. Effects of low doses of caffeine on cognitive performance, mood and thirst in low and higher caffeine consumers. Psychopharmacology (Berl.) 152 (2), 167–173. https://doi.org/10.1007/s002130000506.

Smith, A., 2002. Effects of caffeine on human behavior. Food Chem. Toxicol. 40 (9), 1243–1255.

Smith, P.J., Blumenthal, J.A., et al., 2010. Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. Psychosom. Med. 72 (3), 239–252. https://doi.org/10.1097/PSY.0b013e3181d14633.

Smith, A.P., Christopher, G., et al., 2013. Acute effects of caffeine on attention: a comparison of non-consumers and withdrawn consumers. J. Psychopharmacol. 27 (1), 77–83. https://doi.org/10.1177/0269881112460112.

Temple, J.L., Bernard, C., et al., 2017. The safety of ingested caffeine: a comprehensive review. Front. Psychiatry 8, 80. https://doi.org/10.3389/fpsyt.2017.00080.

Tomporowski, P.D., Tinsley, V.F., 1996. Effects of memory demand and motivation on sustained attention in young and older adults. Am. J. Psychol. 109 (2), 187–204.

Winwood, P.W., Pritchard, H.J., et al., 2019. The competition-day preparation strategies of strongman athletes. J. Strength Cond. Res. 33 (9), 2308–2320. https://doi.org/10.1519/JSC.0000000000003267.