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ABSTRACT

It is well established that caffeine has ergogenic effects on endurance exercise performance. This evidence often comes from well-designed studies in which subjects receive either caffeine or placebo in double-blind, randomized and counterbalanced order. Here, we propose a new methodology which aims to estimate the effects of participant expectancy of ergogenic or anti-ergogenic effects on performance. Sixteen (16) participants performed three (3) 30-minute running tests after being told they would be provided with either a harmful treatment (lactic acid), a beneficial treatment (caffeine) or a placebo. In each blinded case, subjects were given caffeine. The velocity and RPE during the time trial were examined in light of the participant's expectancy before and after the endurance event using Bayesian multilevel models. For pre-exercise expectancy, there is a 92% probability that caffeine expectation decreases RPE (posterior median $\pm$ SD -0.65 ± 0.36) and a 79% probability that lactic acid expectation increases RPE (posterior median $\pm$ SD 0.58 ± 0.47) with expectations for placebo and 'not sure' falling in between (posterior median $\pm$ SD: -0.37 ± 0.32 and -0.22 ± 0.37 , respectively). In general, our interventions suggest an 81% probability that caffeine lowers RPE. However, there was no effect of caffeine supplementation on running velocity (median $\pm$ SD 0.04 ± 0.08 km.h⁻¹). We concluded that when a participant believed they are under a potentially positive treatment, their RPE decreased but if they believed themselves to be under a harmful treatment, their RPE increased, regardless of the actual positive intervention; neither caffeine nor the expectancy of a particular intervention improved actual performance as measured by running velocity in a 30-minute period.

Keywords: Caffeine, Endurance, Expectancy, Ergogenic Aid

Abbreviations:

RPE: rating of perceived exertion

INTRODUCTION

Very few of claimed ergogenic aids have a strong evidence base (Burke, 2017); however, caffeine is generally accepted as an ergogenic aid during endurance exercise (Pereira *et al.*, 2016; Silveira *et al.*, 2017). This evidence comes from well-designed studies in which subjects receive either ergogenic aid or placebo in a randomized and counterbalanced order and double-blind manner. Subjects are expected to have better performance under treatment condition than placebo or control. However, recent studies have shown that when a subject believes that he had consumed an ergogenic aid, his performance is increased regardless of placebo or ergogenic aid consumption (Saunders *et al.*, 2016; Brietzke *et al.*, 2017; Hurst *et al.*, 2017). For example, when a subject is engaged in crossover counter-balanced research, they have a 50% change of receiving a placebo or active treatment; however, the subject could receive a placebo and had the expectancy to receive the active treatment or have doubt regarding what they are receiving. This doubt or expectation (positive or negative) can have a psychological effect on the outcomes, improving, decreasing or nulling the effect (Foad *et al.*, 2008; Brietzke *et al.*, 2017; Lindheimer *et al.*, 2019). Hence, the chance of receiving the treatment or placebo is quite different from the subject's expectancy, and the expectancy has a direct role in the psychological mechanism of placebo and nocebo effects (Benedetti, 2008; Brietzke *et al.*, 2017; Lindheimer *et al.*, 2019), challenging the traditional double-blind studies applied to verify the treatment effects (Kirsch & Weixel, 1988). Therefore, the methodology applied in these previous studies was designed only to test the hypothesis of a different result between ergogenic aid and placebo, promoting a positive expectancy instead of a neutral expectancy. The neutral expectancy is aimed to obtain a real physiological effect of a treatment (i.e., without a strong psychological interference).

We believe that suggesting the use of a harmful supplement for performance when the subject is consuming a theoretically beneficial supplement, is a good way to prove a real efficiency (or not) of supplements on human performance and the influence of the expectation on the outcome. The methodology proposed here is different from nocebo concept in which subjects believe that they are consuming a harmful substance but are consuming an inert substance for performance, neither negative nor positive (Colloca & Finniss, 2012). Thus, we believe that this new methodology is very promising to evaluate the real efficiency of some ergogenic aids and expectation, which could help with the evidence-based use of these strategies to improve human performance.

Therefore, the current study applies a new methodology to examine the current paradigm that caffeine supplementation has a beneficial effect on human performance. We aimed to verify the effect of caffeine and expectation on endurance performance and RPE.

MATERIALS AND METHODS

Experimental Design

To test this new methodology, we recruited 16 physically active subjects, 7 women and 9 men (weight: 70.7 ± 12.9 kg; height: 1.71 ± 0.1 meters; age: 31.5 ± 7.5 years old). The participants came to the laboratory 5 times: a) familiarization; b) 30-minutes of running as a control (without caffeine); c) three different experimental sessions of 30- minutes of running when the subjects were submitted to the treatments (i.e., caffeine in all three sessions). The participants were informed that they could be ingesting either caffeine, placebo or lactic acid. We did not make suggestions of what they could be consuming. Nevertheless, they consumed the ergogenic aid that improves performance (according to the current evidence) in all experimental sessions (i.e. all sessions except for familiarization and control). All subjects gave written informed consent following the Declaration of Helsinki. The protocol was approved by the local Ethics Committee (protocol number: 2.795.798).

All tests were performed on a treadmill (Inbrasport Super ATL). We instructed the subjects to perform their best over a 30-minute run, trying to achieve the longest possible distance. Previous studies with similar trial duration have shown a performance improvement using caffeine (Gliottoni *et al.*, 2009; Hodgson *et al.*, 2013; Saunders *et al.*, 2016; de Souza Gonçalves *et al.*, 2017). The subjects consumed a caffeine supplement 60 minutes before running, with a dosage of 6 mg/kgBM (McLellana *et al.*, 2016; Pereira *et al.*, 2016). This study was blind for volunteers. The investigators were not blinded.

Familiarization

On the first visit to the laboratory, we familiarized subjects with the procedures. They ran 30 minutes without performing their best. They could increase and decrease speed freely. We explained the Rating of Perceived Exertion scale (RPE) before running and displayed the scale during the run in the same manner performed in the control and experimental sessions. We informed the subjects that the objective of this study was to know if: a) caffeine improves performance; b)

lactic acid decreases performance; c) what would be the percentage of increase and decrease. When the study ended, we revealed the aim of the research and what they had consumed in all sessions.

Trials

The subjects ran in four sessions in which they were instructed to cover the longest distance possible within a 30-minute period. First, they ran 30 minutes without consuming any supplement (control trial). Whenever desired, the subjects could increase or decrease the velocity during the run, being allowed to have an end spurt, simulating a real competition. In all trials, the subjects were not provided feedback regarding the current distance covered in the session. Sixty minutes before the second, third and fourth trials, the subjects consumed a caffeine supplement but were informed that they could be ingesting either placebo, caffeine or acid lactic. They were then instructed to try and cover a longer distance than control trial. All sessions were preceded by 5 minutes of warm-up at a self-selected velocity. The time between each session/trial was 7 days. The volunteers completed all trials at the same time of the day to avoid circadian rhythm influence.

Caffeine Supplementation

Subjects ingested pure caffeine (6-mg kg⁻¹ body mass) (Desbrow *et al.*, 2012; Pereira *et al.*, 2016) in capsules with 250 mL of water 60 minutes before the time trial (Goldstein *et al.*, 2010). We did not control the caffeine consumption habits because it does not influence performance (de Souza Gonçalves *et al.*, 2017).

Evaluation of the Rate of Perceived Exertion

All subjects reported overall perceived exertion using the Borg scale (6–20 points) (Borg, 1982) at minute 10, 20 and immediately at the end of running.

Questionnaires

In each supplementation trial, subjects were required to respond to a standardized question immediately before exercise (i.e., 1-h post-caffeine ingestion) and again immediately after running. The question was: “Which supplement do you think you have ingested?”. They had the following options to choose from: (a) Caffeine; (b) Placebo; (c) Lactic Acid; (d) Don’t Know. They could choose the same answer every time they were asked (e.g., caffeine before exercise on trial 1 and 3) if they wanted. We also asked the reason why they had chosen their answer.

Data Reduction and Statistics

For each exercise session (control and three experimental sessions), RPE and running velocity were averaged across the trial. For some analyses, all three experimental sessions were reclassified simply as “Caffeine” so as to compare the general effects of caffeine, regardless of expectancy, against control. In other analyses, the experimental trials are broken out by the participant’s expectancy of the intervention either pre-trial or post-trial. For analyses assessing the overall effect of caffeine on velocity or RPE, a Bayesian random-intercept (randomized at the participant-level) multilevel model was utilized. For analyses where the effect of pre-trial or post-trial expectancy is used to estimate running velocity or RPE, a Bayesian multilevel model with a random intercept and random slope at the participant level was utilized. In this case, the slopes for a participant were allowed to vary based upon the true session type (control or caffeine), since it is reasonable to expect that a true physiological effect of caffeine should be modeled differently than a control session.

In each Bayesian multilevel model, the R programming language (version 3.5.2) (Team, 2018) was used to interact with the STAN Bayesian engine via the rstanarm R package (Goodrich B *et al.*, 2018) . In the case of each model, the default weakly informative priors were used (i.e. after centering and scaling: intercept= normal distribution, center: 0, scale:10; coefficients: normal distribution, center: 0, scale: 2.5; sigma/error: exponential distribution, rate= 1; covariance matrix: decov, regularization= 1, concentration= 1, shape= 1, scale= 1) , 4 sampling chains were used with 2000 iterations, half of which constituted the “warm-up” and were not used for posterior analysis. For each model, it was verified that the R-hat was less than 1.05 and the Monte Carlo standard error was less than 5%, ensuring model validity. Posterior predictive checks and histograms of residuals were both examined to ensure the models conformed to the assumptions of constant variance and residual normality. All images are created using the ggplot2 and bayesplot packages (Wickham, 2016; Gabry J & Mahr T, 2019).

RESULTS

Running Velocity

There was no discernable general effect of caffeine supplementation on running velocity (Figure 2, Pooled Caffeine posterior median $\pm$ SD 0.04 $\pm$ 0.08 km.h⁻¹). Similarly, model posterior distributions representing participant expectations of the intervention pre-trial and post-trial do not suggest a meaningful effect on running velocity (i.e. all posterior distribution medians are near zero and 80% credible intervals contain zero; see Figures 3 & 4).

RPE during Running

The posterior credible intervals for the coefficient representing the general effect of caffeine on RPE suggest an 81% probability that caffeine lowers RPE, though the magnitude is modest (posterior median $\pm$ SD -0.32 $\pm$ 0.23; Figure 5). When considering the effects of participant expectations on RPE, the magnitudes are modest but suggest a robust response in line with what one might expect based on previous literature (Figures 6 and 7). For pre-exercise expectancy, there is a 92% probability that caffeine expectation decreases RPE (posterior median $\pm$ SD -0.65 $\pm$ 0.36) and a 79% probability that lactic acid expectation increases RPE (posterior median $\pm$ SD 0.58 $\pm$ 0.47) with expectations for placebo and ‘not sure’ falling in between (posterior median $\pm$ SD: -0.37 $\pm$ 0.32 and -0.22 $\pm$ 0.37, respectively). The results for post-exercise expectancy are similar to pre-exercise (Figure 7) with a 96% probability that caffeine expectation decreases RPE (posterior median $\pm$ SD -0.68 $\pm$ 0.31).

Qualitative assessment for rationale why subjects selected their answer

When the subjects felt less tired, more agitated, nauseated, and had a perception of performance improvement they chose the “caffeine” option; however, when they felt more tired, cramps symptoms, heavy legs and a perceptions of worse performance they chose “lactic acid” option; and when they had neutral feelings they have chosen “I don’t know” or “placebo” options.

DISCUSSION

The method used here to evaluate the effectiveness of caffeine suggests that the primary effect of caffeine is on RPE and not in endurance performance. The main results were that: 1) When a participant believed they are under a potentially positive treatment, their perceived exertion decreased but if they believed themselves to be under a harmful treatment, their perceived exertion increased, regardless of the actual positive intervention; 2) neither caffeine nor the expectancy of a particular intervention improved actual endurance performance as measured by running velocity in a 30-minute period. Therefore, the physiological effect of caffeine has a modest effect on RPE, which is synergistic with positive expectancy (more pronounced decrease on RPE). However, a negative expectancy is more potent than the physiological effect of caffeine on RPE formation, leading to an RPE increase. Neither caffeine (physiological action) nor expectancy (psychological response) was able to improve endurance performance as measured by changes in velocity.

The volunteers did not improve the covered distance during 30 minutes of running (a function of average velocity) with caffeine supplementation. We expected an improvement greater than 3%, which represents the smallest worthwhile change in performance (Hopkins, 2004). However, we observed that caffeine supplementation did not have an ergogenic

effect in this regard. Previous research using an RCT was able to induce a performance improvement in endurance exercise (Pereira *et al.*, 2016; Silveira *et al.*, 2017) mainly attributed to a decrease in RPE (Marcora & Staiano, 2010). As our protocol was time-limited (30-minutes of duration), the anticipatory mechanism likely modulated the performance previously (Ulmer, 1996), maintaining the velocity average among the trials. It is possible that the protocols with time to exhaustion could have different outcomes being modulated by the subject's expectation. We believe that the performance improvement in previous studies was due to a psychological effect caused by RCT (Pereira *et al.*, 2016; Silveira *et al.*, 2017) (i.e., positive expectations) and not by the physiological effect of caffeine supplementation as previously stated (Graham, 2001). When an individual consumes caffeine and improves performance, it is assumed that caffeine acts on metabolism, skeletal and cardiac muscle, as well as the central nervous system. However, our data do not support the notion that caffeine *per se* improves endurance performance.

The action of caffeine modulating lipid metabolism through greater lipid oxidation is controversial, with studies showing an increase (Costill *et al.*, 1978; Olcina *et al.*, 2012) and others showing no change in metabolism (Pereira *et al.*, 2016). It is suggested that caffeine modulates positively catecholamine's release, which could promote greater lipid mobilization from adipose tissue and intramuscular stock (Costill *et al.*, 1978; Olcina *et al.*, 2012). However, based on the present study, if the lipid mobilization is greater when caffeine is consumed 60 minutes before aerobic exercise with 30 minutes duration, it does not modulate performance positively.

Caffeine action on the central nervous system is the most accepted mechanism of performance improvement. Caffeine would interact with adenosine receptor type I (A₁ receptor) decreasing the perceived exertion sensation and improving performance (Doherty & Smith, 2005a) at the spinal and supraspinal level, increasing the central nervous system excitability (Tarnopolsky, 2008). Recently the caffeine mouth rinse was shown as having an ergogenic action improving cognitive (De Pauw *et al.*, 2015) and exercise performance (Bottoms L *et al.*, 2014), likely through the link between buccal mucosa and the brain, or, in our understanding, through the positive expectations about the caffeine effect, challenging the caffeine action on A₁ receptor. As RPE is a conscious feeling of how hard a physical exercise is, the decrease in a RPE, regardless of which cause it, could explain the performance improvement. Caffeine decreased RPE by 5.6% in the previous study (Doherty & Smith, 2005b). In our study the caffeine consumption induced a modest RPE decrease (-0.32), with 81% of probability to observe this decrement, regardless of the expectations. It has been suggested that RPE arises from neurocognitive processing of corollary discharges from premotor and motor areas and that caffeine consumption prior to

exercise activity in these areas (de Morree *et al.*, 2014); however, this hypothesis has been disputed (Pires *et al.*, 2018; Franco-Alvarenga *et al.*, 2019).

In this study, we show that RPE decrement is generally dependent on positive belief (-0.65). When a subject believed they had consumed caffeine, RPE was lower than when they believed have consumed lactic acid or in control trial. If the subject believes that they are receiving caffeine, it will probably decrease perceived effort (92% probability) (Brietzke *et al.*, 2017), similar to studies with a caffeine mouth rinse.

The role of lactic acid on performance is believed by the general population to cause fatigue and pain, though we know that lactate is not the cause of fatigue and acidosis (Robergs *et al.*, 2004). We used this paradigm to induce a negative expectation on the volunteers. The present methodology was able to induce a negative expectation and promoted an increase (+0.58) in RPE compared with control trial, which is in the opposite direction of the current literature when the subject's consume 6 mg/Kg of caffeine (Pereira *et al.*, 2016). The data show a 79% probability that expecting to consume lactic acid increases RPE even when caffeine is ingested, suggesting that expectancy is more important than physiological caffeine consumption on RPE. However, neither positive nor negative expectations modulate endurance performance.

When subjects reported that they have consumed a placebo pill or have doubt about what was ingested, RPE and performance do not change. It is what a scientist hopes when applying a placebo-controlled study. However, previous studies have shown a performance improvement and RPE decrease in a placebo group (Beedie *et al.*, 2006; Beedie, 2010; Pires *et al.*, 2018). The primary interpretation of these findings is the called "placebo effect". The placebo effect is when the effect expected only for a treatment group is observed in the placebo group (e.g., performance improvement) (Benedetti, 2008; Beedie & Foad, 2009; Beedie, 2010). The explanation is that the psychological effect of a positive expectancy promoted the beneficial effect on placebo group (Benedetti, 2008; Beedie & Foad, 2009). Our data shows that the RCT may not be the is not the best choice to verify the treatment efficacy, like sports supplements. On the methodology applied here, we could see that when a subject perceives a treatment as a placebo, the outcome was what is expected with RCT placebo-controlled.

Gathering all our results and literature data discussed above, it is likely that previous studies showing a positive effect of caffeine supplementation on performance observed this effect because of positive expectancy and that these results are thus protocol-specific. Indeed, studies that abolished the expectancy of positive effect on their methodology had a trivial

impact on performance (Hurst *et al.*, 2017). Here the subjects consumed caffeine in all trials, but we promoted some doubts in the subject's thoughts about the treatment suggesting that they could have consumed a harmful supplement (lactic acid). It could have abolished the positive expectancy of performance improvement. Therefore, the expectancy is likely to be more critical to performance improvement than caffeine effect on the physiological system. The option chosen the most was placebo, possibly reflecting the doubt caused by the methodology; it is essential to the new method proposed here because the positive expectancy was abolished and we were able to investigate the real effect of caffeine on physiological system and performance, which does not happen with RCT methodology. When questioned about which supplement they thought they had ingested before the caffeine-related test volunteers reported: "I'm less tired," "I'm agitated," "I'm nauseated"; "I don't know," and placebo-related volunteers reported: "I didn't feel any physiological effect." When questioned about which supplement they thought they had ingested after to the caffeine-related test volunteers reported: "I felt less tired", "I think performance has improved", "I'm nauseated"; acid lactic-related volunteers reported: "My legs were heavy", "I think performance was worse", "I had cramps symptoms" and "I don't know," and placebo-related volunteers reported: "I didn't feel any physiological effect". All these feelings are connected to people's belief that consuming caffeine beneficial effects on performance or believing in a harmful effect of lactate.

CONCLUSION

We conclude that RPE is modulated by caffeine ingestion and person's expectation (positive, neutral or negative belief) about the treatment efficacy. Therefore, if one believes that they have consumed caffeine, an accepted ergogenic pill, it will potentially decrease RPE; if one believes that they have consumed a placebo (neutral treatment), it will have a neutral effect on RPE, corroborating our premise that randomized placebo-controlled studies induce an increment on positive expectancy. On the other hand, if one believes that they have consumed lactic acid, an accepted ergolytic product of metabolism, it will increase RPE. However, neither caffeine consumption nor expectancy (positive, negative or neutral) influenced performance in the current study. The data show that RPE is a consequence of the interaction between physiological systems and psychology (expectancy).

The authors declare no conflict of interest.

This publication has been approved by all co-authors.

PA conceived and designed research. MO, PP, KT and GE conducted

experiments. MT analyzed data. PA and MT wrote the manuscript. All authors read and approved the manuscript.

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Figures

Fig. 1 Schematic Overview

Fig. 2

The posterior distributions for the multilevel Bayesian model assessing the effect of pooled caffeine effects on running velocity. The blue line in the middle of the distribution is the median and the shaded area are 80% credible intervals. In this case, the intercept represents a non-caffeine condition.

Fig. 3

The posterior distributions for the multilevel Bayesian model assessing the effect of intervention expectation pre-exercise on running velocity. The blue line in the middle of the distribution is the median and the shaded area are 80% credible intervals.

Fig. 4

The posterior distributions for the multilevel Bayesian model assessing the effect of intervention expectation post-exercise on running velocity. The blue line in the middle of the distribution is the median and the shaded area are 80% credible intervals.

Fig. 5

The posterior distributions for the multilevel Bayesian model assessing the effect of pooled caffeine effects on RPE. The blue line in the middle of the distribution is the median and the shaded area are 80% credible intervals. In this case, the intercept represents a non-caffeine condition.

Fig. 6

The posterior distributions for the multilevel Bayesian model assessing the effect of intervention expectation pre-exercise on RPE. The blue line in the middle of the distribution is the median and the shaded area are 80% credible intervals.

Fig. 7

The posterior distributions for the multilevel Bayesian model assessing the effect of intervention expectation post-exercise on running velocity. The blue line in the middle of the distribution is the median and the shaded area are 80% credible intervals.