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Acute Effects of Caffeine on Dynamic Accommodative Response and Pupil Size: A Placebo-controlled, Double-blind, Balanced Crossover Study

Beatriz Redondo, Jesús Vera, Carmen Carreño–Rodríguez, Rubén Molina-Romero, and Raimundo Jiménez

Department of Optics, Faculty of Sciences, University of Granada, Granada, Spain

ABSTRACT

Objectives: To evaluate the acute effect of caffeine consumption on the accuracy and variability of accommodation, as well as its impact on pupil size and perceived levels of activation.

Methods: 22 university students (21.68 ± 3.67 years old) ingested a capsule of caffeine (4 mg/kg) or placebo (300 mg of corn-starch) in two different days and counterbalanced order. After 30 min of capsule ingestion, we objectively measured the accuracy and variability of accommodation, and pupil size using the WAM-5500 binocular open-field autorefractometer for 2 min at each of the six viewing distances (5 m, 50 cm, 40 cm, 33 cm, 25 cm, and 20 cm). Subjective levels of activation to check the effectiveness of caffeine/placebo manipulation were also reported.

Results: We found that after 30 min of caffeine/placebo ingestion, participant perceived higher levels of activation in the caffeine condition (p = .047, Cohen´s d = 0.48). Caffeine consumption induced a statistically significant dilator effect on pupil size (p = .011, η^2 = 0.271), and reduced variability of accommodative response (p = .027, η^2 = 0.211). However, no differences were obtained for the accuracy of accommodation (p = .321).

Conclusions: Our data suggest that caffeine consumption reduced the variability of accommodative response and induced pupil dilation. Nevertheless, the accuracy of accommodation was insensitive to caffeine intake. These findings may be explained by the bidirectional relationship between ocular functioning and the nervous system´s state of activation.

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Introduction

Caffeine is the most widely consumed psychoactive drug.[1] It is rapidly distributed throughout the body, increasing energy metabolism in the brain at the same time that decreases cerebral blood flow.[2] Caffeine predominantly acts on the cerebral circulation as an adenosine antagonist, which is a central nervous system modulator that generates neural and vascular effects.[3] Also, caffeine has demonstrated to be an effective ergogenic aid to improve cognitive performance,[4] and promotes physiological and behavioural changes in humans.[5] The ingestion of caffeine leads to different physiological adaptations such as blood pressure rise as a result of a greater vascular resistance of the vessels, increased myocardial stimulation, and reduced heart rate and tone of smooth muscle.[6]

In addition to these physiological responses induced by acute caffeine intake, direct vasoconstriction of several intracranial arteries such as ophthalmic, central retina, and short posterior ciliary arteries has been described, altering the ocular physiology.[7] Indeed, there are numerous ocular parameters that are sensitive to caffeine intake (e.g., blood flow in the optic nerve head,[8] choroidal thickness,[6,8] intraocular pressure,[9] tear formation,[10] ocular aberrations,[11] eye movements,[12] visual processing,[13] pupil size,[11] and accommodative function.[14]) The physiological mechanisms underlying caffeine effects on the visual system have been commonly explained by the bidirectional relationship between ocular functioning and the parasympathetic and sympathetic branches of the autonomic nervous system (ANS).[15] In this regard, caffeine as a stimulant of the central nervous system,[16] promotes physiological variations by the activation of the sympathetic branch,[17] at which different ocular indices (i.e., intraocular pressure, oculomotor system, accommodative response) have demonstrated to be sensitive.[18]

In relation to accommodative function, Abokyi et al. (2016)[14] found that ingesting a caffeinated drink of 250 mg increased the amplitude of accommodation in comparison to placebo consumption, these effects being probably mediated by the stimulation of the ANS.[16] However, these authors analysed the monocular amplitude of accommodation by the push-up technique, and despite this method is widely used in clinical practice, there is no agreement on its accuracy in research settings due to its subjectivity.[19,20] In addition, the amplitude of accommodation is the greatest increase in refractive change that an eye can achieve in adjusting its focus. This measure is often evaluated by increasing the accommodative demand by either moving the target closer to the subject or by increasing minus lens powers.[20] For its part, the accommodative response (AR) is a measure of the accuracy of the accommodative system. If the AR is lower than the accommodative demand is termed as lag of accommodation, whereas if the AR is greater than the accommodative demand is described as lead of accommodation. There is evidence that as the accommodative demand increases, the AR

CONTACT Jesús Vera jesusvv@correo.ugr.es Department of Optics, University of Granada, Campus de la Fuentenueva 2, Granada 18001, Spain
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becomes less accurate resulting in a greater accommodative lag.[21] It has been suggested that if subjects meet ~70% of the accommodative demand, they perceive the target clear.[22] The clinical relevance of AR relies on its implication when focusing on all distances, whereas the amplitude of accommodation is only relevant when looking at extremely near targets, and thus, the importance of an increased amplitude of accommodation is somewhat limited. Importantly, the autonomic control of AR is predominately mediated by parasympathetic innervation, but also by the sympathetic activity.[23–25] An increase in parasympathetic innervation of ciliary smooth muscle produces a rapid (1–2 s) and substantial positive accommodation, whereas sympathetic input is inhibitory in nature (reduces accommodation), acts relatively slow (20–40 s) and leads to small changes (less than – 2 D).[15,26,27] The balance of the neural integrator of accommodation determines the accuracy of AR.[23,28,29] Also, when focusing on a stationary target AR is constantly varying over time with a temporal instability of about ± 0.5 D, aiming to maintain AR and obtain directional cues for the dynamic AR.[30] This characteristic is termed accommodation variability, and it is produced as a combination of neurological control and physiological rhythmic variations,[31] being termed as variability or microfluctuations of AR.[30] Previous studies have proved that AR is sensitive enough to experience alterations under increasing cognitive demand or changes in the level of arousal due to mental fatigue,[29,32–35] predominantly attributable to variations of the ANS activity.[35,36] Even though it is well established that caffeine stimulates the ANS, the potential impact of caffeine intake on the dynamics of AR remains unclear.[37]

As stated above, effects of caffeine on ANS activity are well known,[17] and thus, it is plausible to expect that AR, which is dependent of ANS innervation, may be altered by caffeine intake. To assess the possible impact of acute caffeine consumption on AR, participants ingested either a caffeine or placebo capsule, and 30 min later, we objectively obtained the accuracy and variability of AR using a binocular open-field autorefractometer (WAM-5500 Grand Seiko Co., Ltd., Hiroshima, Japan), which has demonstrated to be an accurate tool for quantifying AR.[38] The main objectives of this placebo-controlled, double-blind, balanced crossover study were to evaluate the acute effect of caffeine consumption on the accuracy and variability of accommodation.[38] In addition, given the accommodation-pupil synkinesis in near response,[39] we explored the influence of caffeine intake on pupil diameter. To check the effectiveness of caffeine/placebo manipulation, participants reported their subjective levels of activation. Based on the available literature, we hypothesized that the accuracy of AR and pupil size would increase in the caffeine condition,[14] whereas accommodative variability would decrease as a consequence of a higher sympathetic activation after consuming caffeine.[30] We expect that participants perceive higher levels of activation after caffeine consumption.[16]

Methods

The protocol was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the University Institutional Review Board (IRB approval:438/CEIH/2017).

Participants

Twenty-two (10 women and 12 men) healthy undergraduate students were recruited to participate in this study. The experimental sample had an age range between 18 and 28 years (mean age±standard deviation [SD]: 21.68 ± 3.67 years old) and a weight range between 50 and 84 kg (mean weight ±standard deviation [SD]: 66.70 ± 9.84 kg). The habitual caffeine intake of the participants ranged between 0 and 4 cups of caffeine per day (mean consumption±standard deviation [SD]: 0.74 ± 1.19 cups per day). At the initial visit, an optometrist performed an optometric examination which included: distance and near monocular and binocular best-corrected visual acuity (VA), objective refraction using the Grand Seiko WAM-5500 autorefractometer (Grand Seiko Co. Ltd., Hiroshima, Japan), monocular, and binocular non-cycloplegic subjective refraction, accommodative push-up amplitude, monocular and binocular accommodative facility using ±2.00D flippers at 40 cm, near and distance horizontal and vertical phoria measured by the Thorington's method, negative and positive fusional vergence at 40 cm and far using a prism bar, near point of convergence, and near stereoacuity with the Randot Stereotest (Stereo Optical Company, Chicago, Illinois). Binocular and accommodative test procedures and normative values followed the recommendations of Scheiman & Wick (2008).[40] The inclusion criteria considered to participate in this study were: (1) have a corrected VA≤0.0 logMAR (20/20 Snellen) in each eye, (2) present low visual discomfort (cut-off value<24) as measured by the Conlon survey,[41] (3) be free of strabismus, amblyopia, or any ocular disease, (4) have a near stereoacuity better than 50 s of arc, and (5) have an uncorrected spherical equivalent refractive error lower than ±1D. All participants were no smokers and they had no history of cardiac arrhythmia, peptic ulcer disease, liver or kidney damage, allergy to xantic bases, insomnia, pregnancy, or breastfeeding.[42]

Accommodative response assessment

For the study of dynamic accommodation, we objectively obtained the refractive state of the eye at different viewing distances using the clinically validated Grand Seiko WAM-5500 open field autorefractometer in binocular conditions and HI-SPEED mode, which offers continuous recording at a rate of ~5 Hz.[38] Data were recorded in binocular conditions from the dominant eye which was determined by the hole-in-the card method,[43] and refractive state and pupil size were recorded with a sensitivity of 0.01 D and 0.1 mm, respectively. Subjects were seated at the instrument with their head stabilized in the chin rest and forehead strap and were aligned with the fixation target which was positioned in the participant's gaze midline. Participants maintained in focus a high-contrast (Michelson = 79%) five-point back star on a white background target at six viewing distances (5 m, 50 cm, 40 cm, 33 cm, 25 cm, and 20 cm) during a time period of 2 min for each one. The order of the distances measured was randomized, and 3-min breaks between measurements were established in order to avoid the effects of sustained accommodative or convergence effort on tonic accommodation.[44] After 30 min of caffeine/placebo ingestion,

we first performed a monocular static refractive measure at far in both compensated eyes (baseline refractive value), and subsequently, the assessment of dynamic AR at the distances tested was carried out. The base luminance of the target was 31 cdm−2, and the experimental room illuminance was ~150lx.

For the elimination of blinking or recording errors, we identified and removed data points of ±3 standard deviations from the mean spherical refraction value.[45] Then, we obtained the values of accuracy and variability of accommodation, and pupil size from the remaining data. Following the equation proposed by Poltavski et al., (2012),[46] the accuracy of accommodation was calculated by subtracting the mean value from the dynamic measures to the accommodative demand at each distance. This value was also corrected for the residual refractive error at far distance, using a baseline static measurement taken at each experimental session. The standard deviation during each dynamic AR measurement was considered for the variability of accommodation.

Subjective questionnaires

At the beginning of each experimental session, participants completed the Stanford Sleepiness Scale (SSS), which assess the subjective level of alertness/sleepiness.[47] This scale contains seven statements ranging from 1 "Feeling active, vital, alert, or wide awake" to 7 "No longer fighting sleep, sleep onset soon, having dream-like thoughts", and participants have to indicate which statement reflects their actual state. After 30 min of caffeine/placebo ingestion, we asked participants to complete a visual analogue scale in order to evaluate their subjective level of activation (0 absolutely not activated and 10 extremely activated).

Procedure

The experiment was conducted in three separate sessions, which were performed on different days and were scheduled at the same time of day (±1 h). In the first session, the optometric examination was performed to exclude those participants who did not fulfil the inclusion criteria, and also, we asked participants to report their daily consumption of caffeine. Participants were asked to wear their soft contact lenses when necessary, and they were used in the different experimental sessions. Before attending the laboratory, participants were instructed to sleep at least 7 h the night prior testing, to avoid the practice of intense physical activity 2 days prior the testing session, as well as alcohol and caffeine-based drinks 24 h and 12 h before each experimental session, respectively.

A pharmacist laboratory (Acofarma distribución S.A., Madrid, Spain) prepared the caffeine-containing capsules (caffeine anhydrous and corn-starch) and placebo capsules (corn-starch), the contents of which were certified safe for human consumption. Both capsules (placebo and caffeine) had an identical colour, size, and shape, and thus, they were indistinguishable. In the main experimental sessions, a capsule of caffeine (4 mg/kg of caffeine plus 20 mg of corn-starch) or placebo (300 mg of corn-starch) along with 100 ml of tap water was orally administrated in a counterbalanced order. Caffeine capsules were available in steps of 20 mg, and thus, participant´s weight was rounded up in steps of 5 kg in order to choose the amount of caffeine used by each individual. The amount of caffeine given to the participants ranged between 200 mg to 340 mg (mean caffeine ± standard deviation [SD]: 243.18 ± 87.94 mg). Aiming to accomplish the double-blind procedure, the capsules were prepared and coded by a third person. After caffeine or placebo consumption, participants were allowed to rest for 30 min in order to reach a considerable plasma concentrations of caffeine.[48]

Statistical analysis

A Shapiro–Wilk test and Levene's test were performed to assess the normality of data and the equality of variance, respectively ($p > .05$). Aiming to check possible differences in the level of alertness/sleepiness at the beginning of both experimental sessions, a t-test for related samples was performed for the SSS survey. Also, a t-test for related samples with caffeine consumption (placebo, caffeine) as the only within-participants factor was carried out for the perceived level of activation reported by participants after 30 min of ingesting either caffeine or placebo. For the main statistical analyses, separate two-ways repeated measures ANOVA with caffeine consumption (placebo, caffeine) and target distance (far, 50 cm, 40 cm, 33 cm, 25 cm, and 20 cm) as the within-participant factors, and using the measures of AR (accuracy and variability) and pupil diameter as the dependent variables, were performed. Multiple comparisons were corrected using the Holm-Bonferroni procedure. Statistical significance was set at 0.05, and standardised effect sizes were reported by means of the partial η^2 for Fs and the Cohen's d for t tests. All statistical analyses were carried out using the JASP software (version 0.9.0.1).

Results

Manipulation check and caffeine effects on subjective activation

First, we analysed the perceived level of alertness/sleepiness at the beginning of each experimental session by the SSS survey. Our analysis revealed no statistically significant differences between both experimental sessions ($p = .815$), confirming that participants came to the laboratory under similar conditions. Then, the perceived level of activation demonstrated higher values in the caffeine condition in comparison to the placebo condition ($p = .047$, Cohen´s d = 0.48) (see Table 1).

Influence of caffeine consumption on pupil size

The main effects of caffeine consumption ($F_{1,21} = 7.812$, $p = .011$, $\eta^2 = 0.271$) and accommodative distance ($F_{5,105} = 33.305$, $p < .001$, $\eta^2 = 0.613$) yielded statistical significance, obtaining larger pupil sizes in the caffeine condition in comparison to the control condition, as well as smaller pupil sizes at closer distances. The interaction caffeine consumption x target distance was far from showing any significance ($F_{5,105} < 1$) (Figure 1). Post hoc analysis showed no significant difference

Table 1. Subjective perceived level of arousal and activation response measured before and after the caffeine or placebo intake.

	Placebo Mean (SD)	Caffeine Mean (SD)	p-value
Baseline			
Stanford Sleepiness Scale (SSS; 1–7)	2.05 (0.90)	2.09 (0.81)	0.815
After 30 min of capsule ingestion			
Level of activation (0–10)	6.64 (1.99)	7.55 (1.84)	0.047*

SD= standard deviation, *denotes significant differences between groups ($p < 0.05$).

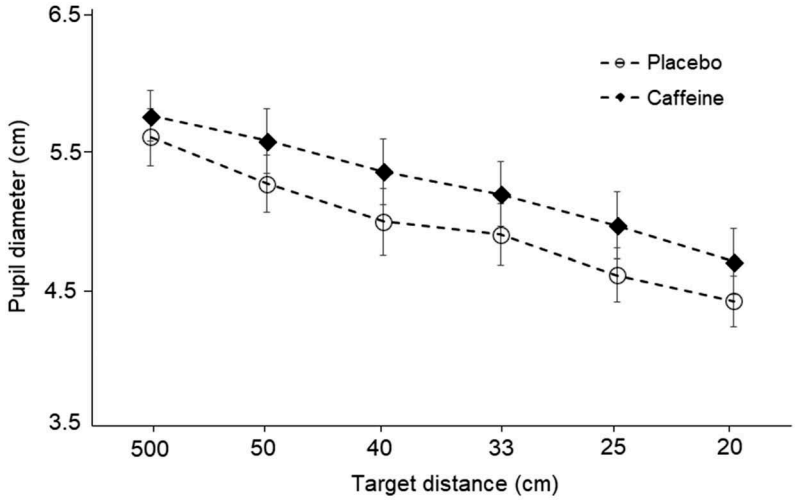

Figure 1. Pupil diameter after caffeine and placebo intake for the different target distances (500 cm, 50 cm, 40 cm, 33 cm, 25 cm, and 20 cm). Error bars show the standard error (SE). All values are calculated across participants (n = 22).

between caffeine and placebo comparisons in each target distance (corrected *p*-value>0.05).

Influence of caffeine consumption on accuracy of accommodation

The accuracy of accommodation shows statistically significant differences for the target distance ($F_{5,105} = 419.780$, $p < .001$, $\eta^2 = 0.977$), showing higher lags of accommodation at closer distances. However, caffeine consumption and the interaction caffeine consumption x target distance did not reach statistical significance ($F_{1,21} = 1.090$, $p = .321$; and $F_{5,105} = 0.412$, $p = .838$; respectively) (Figure 2). Post hoc analysis showed no significant differences for the accuracy of accommodation between caffeine and placebo comparisons for each target distance (corrected *p*-values>0.05).

Influence of caffeine consumption on variability of accommodative response

The analysis of variability of AR showed statistically significant differences for the main factors caffeine consumption ($F_{1,21} = 5.625$, $p = .027$, $\eta^2 = 0.211$) and target distance ($F_{5,105} = 101.683$, $p < .001$, $\eta^2 = 0.829$), as well as for the interaction caffeine consumption x target distance ($F_{5,105} = 4.342$, $p < .001$, $\eta^2 = 0.171$). Caffeine ingestion provoked

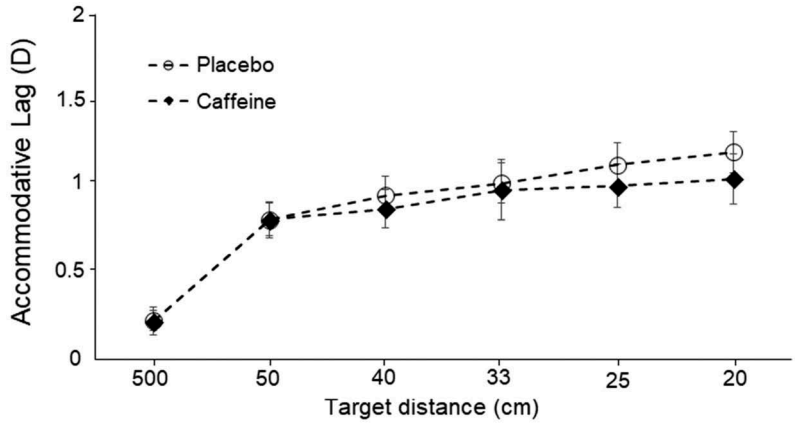

Figure 2. Accuracy of accommodation (lag) after caffeine and placebo intake for the different target distances (500 cm, 50 cm, 40 cm, 33 cm, 25 cm, and 20 cm). Error bars show the standard error (SE). All values are calculated across participants (n = 22).

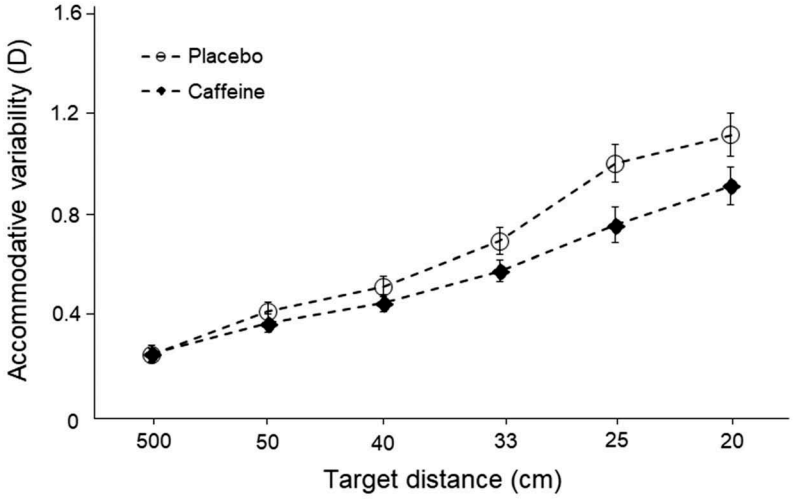

Figure 3. Accommodative variability after caffeine and placebo intake for the different target (500 cm, 50 cm, 40 cm, 33 cm, 25 cm, and 20 cm). Error bars show the standard error (SE). All values are calculated across participants (n = 22).

a better stability of accommodation (lower variability of AR) when compared with the consumption of placebo, and, greater variability of accommodation was found at closer target distances (Figure 3). No significant differences were found in the post-hoc comparisons between caffeine and placebo conditions at each target distance (corrected *p*-values>0.05).

Discussion

Caffeine induces a variety of cardiovascular and central nervous system alterations, which have implications for human behaviour and performance.[4,5,16] The present study aimed to assess the acute effect of caffeine consumption on the visual system, specifically on AR, as well as its impact on pupil size and subjective activation. Our data showed, that under similar pre-experimental arousal conditions, participants reported higher levels of activation after caffeine consumption. We also found that pupil size increased as a consequence of caffeine intake. In relation to AR, the accuracy of accommodation was insensitive to caffeine ingestion, whereas a more stable AR (lower variability of accommodation) was induced by caffeine intake.

According to the subjective responses with the SSS, participants reported a similar level of alertness/sleepiness at the beginning of each session, allowing us to confirm an appropriate experimental control. Regarding the effect of caffeine on subjective feelings of activation, there is a general consensus that acute caffeine consumption causes an increase in perceived arousal/alertness.[16] Our result, in accordance with this fact, indicates that the experimental manipulation was effective in inducing feelings of alertness since participants reported higher levels of activation after 30 min caffeine intake in comparison to the placebo condition.

In agreement with the scientific literature, pupil diameter decreased as the accommodative demand increased.[49] In addition, we found that caffeine induced a mydriatic effect, with a pupil size increment of 5.12% when participants consumed caffeine in comparison to placebo. Although studies on the effect of caffeine on pupil size are inconsistent, our result is in line with Abokyi et al., (2016),[14] who showed pupil dilation after the consumption of a 250 mg caffeine drink. This finding may be explained by the fact that caffeine increases the excitability of the adenosine-sensitive sympathetic nervous system, and thus, heightened sympathetic innervation activity, which results in contraction of the iris dilator muscle, causing pupil dilation.[50] On the contrary, other studies have only found a mydriatic effect of caffeine in non-habitual caffeine consumers,[51] or even, did not find any changes on pupil size.[11] However, those studies used low caffeine doses (lower than 110 mg of caffeine) or did not adjust the caffeine dose to participant´s weight, as we did in the current study, and thus, results from different studies should be cautiously compared.

Higher lags of accommodation (lower AR accuracy) have been linked to reduced attentional resources,[46,52] and since caffeine increases the ability to concentrate and focus attention,[53] it seems reasonable to expect that caffeine would induce a higher AR accuracy. However, we failed to find any effect of caffeine manipulation at the six distances tested (5 m, 50, 40, 33, 25, and 20 cm) on the accuracy of accommodation. To the best of our knowledge, no studies have analysed the accuracy of accommodation under the effects of caffeine using objectives and valid instruments. Here, we used an objective and validated research tool in the study of AR,[38] and thus, our findings are solid in this regard.

We found preliminary evidence of a reduced variability of AR caused by caffeine intake. Accommodative variability occurs during steady-state viewing conditions as a result of the combination of central neurological control and physiological rhythmic fluctuations,[31] and its function aims to maintain an accurate accommodation and obtain directional cues for dynamic AR.[30] The dynamics of the AR is dependent on different factors optical and non-optical factors such as age, monochromatic aberrations, stimulus characteristics, participant´s ametropia, pupil size (e.g., smaller than 3 mm) or individual differences in tolerance of blur and depth of

focus, and thus, altering any of these factors may lead to changes in ocular accommodation.[30,54–56] Both pupil size and accuracy of AR have independent effects on the accommodative variability,[57] with larger pupil sizes being associated with reduced variability of accommodation, while a reduced accuracy of accommodation is linked to higher variability of accommodation.[58] The relationship between accuracy and variability of accommodation is determined by which comparison has been made. Namely, when comparing the variability of accommodation between different accommodative demands, it has shown to increase at greater demands,[59] and also when comparing this variable at the same level of demand, the variability of accommodation increases when the AR is less than the accommodative demand (higher lags).[34] Our data support previous studies since we found that caffeine ingestion induced higher pupil sizes in comparison to the placebo consumption, which has been associated with both reduced depth of focus and variability of accommodation.[60,61] Thus, this mechanism of action may be responsible and justify the decrease found in accommodative variability.

A plausible physiological explanation

We found that caffeine intake (~4 mg/kg) did not meaningfully affect the accuracy of AR, but a reduction in the variability of AR was observed after caffeine consumption. Previous studies suggest that caffeine modulates de ANS activity, which is involved in the ocular accommodation control.[15] As previously stated, caffeine blocks the adenosine receptors and stimulates a reflex activation of the sympathetic system.[2,17] The role of the sympathetic system in the control of accommodation is subtle in comparison to the parasympathetic innervation,[62] however, the sympathetic activity seems to complement the reflexive nature of the parasympathetic activity and slightly affects the dynamics of accommodation, having poor effects on the resting level or amplitude of accommodation.[23] These differences in the role of both ANS branches may explain the lack of changes in the accuracy of accommodation after caffeine consumption. Conversely, sympathetic innervation has been described as necessary to provide optimal accommodative gain across all temporal frequencies and attenuate the retention of accommodative tone induced by periods of intense close work.[62] It is reasonable to consider that this fact may have important implications on the variability of accommodation and explain why caffeine intake induces a better stability of accommodation.

Limitations and future research

A good knowledge of the physiological and functional effects of caffeine on the eye is crucial due to its widespread use. This study provides evidence on the effects of caffeine on accommodation and pupil, showing that caffeine increases pupil size and induces a more stable accommodative response. The current findings may be of interest in research and applied settings. However, there are several factors that may limit the generalizability of our findings, and they should be acknowledged. First, we have discussed different physiological mechanisms that may explain the present findings, however, future studies are needed to determine the role of caffeine on the human structures responsible for ocular accommodation control. We consider that the use of recent developments in ocular imagining techniques (e.g., anterior segment optical coherence tomography) would help to advance into the knowledge of the caffeine effects on the ocular physiology. Also, the measurement of AR with instruments that permit to acquire data at higher frequencies would be of interest in the assessment of some aspects of the dynamics of accommodation (e.g., latency, peak velocity, time-frequency analysis of accommodative fluctuations).[63] Second, some physiological changes induced by caffeine have showed to be dependent on caffeine consumption habits,[17,42] and thus future studies should compare the impact of caffeine intake on AR and pupil size in high and low caffeine consumers. Third, visual fatigue is linked to the accuracy and variability of AR,[45] and we found that the variability of accommodation is sensitive to caffeine ingestion, thus, we consider of interest to test the possible effects of caffeine on visual fatigue by the inclusion of participants with visual discomfort or the design of experiments with prolonged near tasks. Fourth, the impact of caffeine on several physiological indices has showed a dose–response effect,[64] in which low or intermediate doses of caffeine are associated with positive effects (i.e. increase in arousal, concentration, performance), while high doses induce negative effects (i.e. nervousness, agitation).[42] Additionally, peak plasma caffeine concentration is habitually reached between 15 and 120 min after oral ingestion, with a tendency for slightly faster times when lower doses are administered. Here, we choose an amount of caffeine (~4 mg/kg) based on the estimations of mean daily caffeine consumption for US habitual consumers[1] and accommodative measures were assessed between 30 and 60 min after caffeine ingestion. Different doses of caffeine and time frame could lead to a different behaviour of the ocular variables and therefore, the manipulation of caffeine dose and time in future studies may help deepen the association between caffeine and ocular accommodation.

Conclusions

We found an acute effect of caffeine consumption on pupil size and accommodative function, specifically on variability of accommodative response. Our data showed that the ingestion of caffeine provoked a reduced variability of accommodation and induced a dilator effect on pupil size after 30 min of caffeine intake. However, we did not observe any effect of caffeine consumption on the accuracy of accommodation. These findings are in line with the effects of caffeine consumption mediated by binding adenosine receptors and stimulation of the sympathetic nervous system.

Disclosure

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ORCID

Jesús Vera http://orcid.org/0000-0001-8091-2373
Raimundo Jiménez http://orcid.org/0000-0002-8036-2532

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