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Subjective and objective effects of coffee consumption – caffeine or expectations?

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Impact of 5 mg/kg caffeine, chance of receiving caffeine (stimulus expectancies), and expectations of effects of caffeine (response expectancies) on objective (heart rate (HR), systolic/diastolic blood pressure (SBP/DBP), measures of heart rate variability (HRV), and reaction time (RT)) and subjective variables were investigated in a double-blind, placebo-controlled experiment with a no-treatment group. Participants were 107 undergraduate university students (mean age 22.3 ± 3.96 years). Consumption of 5 mg/kg caffeine had an impact on participants' SBP, standard deviation of normal heartbeat intervals, HR (decrease), and subjective experience 40 minutes later even after controlling for respective baseline values, stimulus and response expectancies, and habitual caffeine consumption. No effects on DBP, high frequency component of HRV, the ratio of low- and high-frequency, and RT were found. Beyond actual caffeine intake, response expectancy score was also a determinant of subjective experience which refers to a placebo component in the total effect. Actual autonomic (SBP, HR) changes and somatosensory amplification tendency, however, had no significant impact on subjective experience. Placebo reaction plays a role in the subjective changes caused by caffeine consumption but it has no impact on objective variables. Conditional vs deceptive administration of caffeine (i.e. stimulus expectancies) had no impact on any assessed variable.

Keywords: double-blind versus deceptive administration, caffeine, placebo, blood pressure, heart rate, heart rate variability, expectations

Caffeine is one of the most widely consumed behaviorally active substances in the world, its physiological and psychological effects (e.g. increasing alertness, enhancing vigilance, reducing fatigue, elevating blood pressure) are widely known and utilized (1, 28, 38, 39). Although caffeine acts in several different ways, its most important biological effect is inhibition of adenosin receptors in the brain (1, 32). Pharmacological effects of caffeine are usually well observable in animal models (39). In the case of humans, however, the phenomenon is more complicated: anticipation of caffeine intake and expectations about the effects of caffeine may also play a role in the final response pattern (7, 8, 13, 25). Expectations or expectancies are categorized into three groups (45): (1) *stimulus expectancies* refer to one's belief that he is about to ingest an active substance (in the case of caffeine, these expectancies are triggered, e.g. by taste and smell of coffee); (2) *response expectancies* are expectations about the responses evoked by the drug taken (e.g. the knowledge that caffeine

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elevates blood pressure and improves awareness); and (3) *expectancies* about the *consequences* of the consumption of the given drug (e.g. social consequences of regularly having a coffee with colleagues). According to studies on alcohol, caffeine, and other substances, expectancies often moderate pharmacological effects of psychoactive drugs and can even mimic certain pharmacological effects in the absence of any active substance (i.e. when participants receive placebo (45)).

In addition to sensory stimuli, verbal information has also an impact on stimulus expectancies. In the case of double-blind RCT, participants are informed that they will receive an active substance or placebo, and they are also aware of the likelihood of receiving the active substance (e.g. 0.5 or 0.7) – this is called *conditional* (or *double-blind*) administration (17, 18). From methodological point of view, this way of administration as opposed to *deceptive* administration when patients firmly believe that they receive the active substance (likelihood = 1.0) may lead to underestimation of the magnitude of the placebo effect. Deceptive administration may have a higher external validity, however, it cannot be used in RCTs for ethical reasons.

Caffeine may serve as an appropriate model to investigate this problem as it is legal, widely used, and there exists a placebo (i.e. decaffeinated coffee) that is not easily distinguishable from the active preparation. In an early study (18), individuals receiving caffeine placebo with deceptive information showed higher HR and subjective tension than the conditional information group (no differences in blood pressure were reported). In a second study (17) using a more sophisticated design including groups that received caffeine or placebo with deceptive, conditional, or negative (i.e. participants were told that the drink contained no caffeine) information and measurements 15, 30, and 45 minutes following the administration, effects of information and information-caffeine interactions were found. For example, deceptive information had an impact on participants' alertness 15 minutes after ingestion in both the caffeine and placebo groups, whereas pharmacological effect of caffeine was measurable in the next period. Difference between the effects of deceptive and double-blind information was found in the case of DB, while SBP was only influenced by the actual caffeine intake. In summary, the information given to participants about the likelihood of receiving the active substance (stimulus expectancy) had an impact on certain variables in both the placebo and the caffeine groups. Interestingly, in other studies with placebo-groups only (46, 47) or with placebo and caffeine groups (24), no such differences were found.

In studies that operated with deceptive administration only, mixed and often contradictory results were reported in various cognitive tasks. A synergistic caffeine-information effect was reported in vigilance and psychomotor tasks (8–10), while no or minimal interaction was found in other experiments (7). The manipulation of response expectancies (beliefs about the effects of caffeine) also changed participants' reactions (29), although sometimes in the opposite direction (i.e. stimulant instruction had a negative impact on reaction time) (14).

Abbreviations

BP = blood pressure
DBP = diastolic blood pressure
SBP = systolic blood pressure
HR = heart rate
HRV = heart rate variability
HF = high frequency components of HRV (0.15–0.4 Hz)
LF = low frequency components of HRV (0.04–0.15 Hz)
LF/HF = the ratio of low- and high-frequency power
RCTs = randomized controlled trials
SDNN = standard deviation of normal to normal R-R intervals
SRQ = self-reported questionnare
SSAS = Somatosensory Amplification Scale

Autonomic variables (HR, SBP, DBP) as opposed to subjective variables have usually not been influenced by verbal information about the caffeine content of the drink (12, 21, 36, 42).

In addition to information given to participants, lack of appropriate control group represents a further methodological problem in many studies investigating the placebo effect. Changes in placebo groups are attributable to many factors beyond the genuine placebo-reaction (e.g. natural fluctuations of the given state or symptom, regression to the mean, etc.), thus a non-treated control group (natural history group) is needed to exclude these disturbing factors (4). In many studies investigating the effects of placebo caffeine, no natural history group was included (usually the so-called balanced placebo design was used), and no research has been published to date that studied these effects on groups receiving placebo caffeine or real caffeine with deceptive or conditional information and with a non-treated control group.

The present study aimed to fill this gap and to study the placebo caffeine phenomenon in a complex way. It was hypothesized that actual intake of caffeine and/or higher stimulus expectancies would increase participants' BP, HR, HRV-HF, HRV-LF/HF and reaction time, and would lead to more self-reported caffeine-related symptoms. Moreover, we have hypothesized that peripheral autonomic variables, actual caffeine intake, stimulus and response expectancies, and proneness to amplify subjective symptoms (somatosensory amplification) would have an impact on perceived effects of caffeine.

Materials and Methods

Participants

107 undergraduate university students (mean age 22.3 ± 3.96 years; 39.3% male) volunteered to participate in the experiment. Students received no reward for their participation. Individuals with known cardiovascular problems or caffeine sensitivity were excluded from the study.

Objective measurements

Cardiovascular data (HR, HRV, BP) were recorded. Electrodes were placed to the distal ends of the collarbones and to the anterior superior iliac spines. HR and HRV (SDNN, HF, LF/HF) values were calculated from one-minute intervals of resting sessions, SBP and DBP were measured at the end of the resting sessions. Reaction time measurement was carried out using the PsychLabWin v1.1 software. The measurement consisted of 90 trials, it took approximately 5–7 minutes to complete.

Questionnaires

Habitual caffeine consumption were assessed using a single question ("How often do you drink a coffee?") to be rated on a 5-pont Likert-scale (*never/sometimes/several times a week/ once a day/several times a day*).

Expectancies about the effects of coffee (response expectancies) and actually experienced effects were measured using the SRQ-scale developed by Rush (15, 34). The SRQ assesses the existence of sixteen psychic (e.g. alertness, concentration) and somatic (e.g. palpitation, headache) caffeine-related symptoms on a 4-point Likert-scale (*not at all/a bit/to great extent/extremely*). In the case of T1 (baseline) and T2 measurements, participants were asked to rate the actual severity of the symptoms and conditions, while they had to mark expected severity of symptoms in the expectancy measurement. Internal consistency (Cronbach's alpha coefficients) of the scale was between 0.72 and 0.80.

Proneness to amplify perceived symptoms was assessed by the 10-item SSAS (3). Somatosensory amplification refers to the tendency to experience somatic sensations as intense, noxious, and disturbing. The Hungarian version proved to be psychometrically sound in previous studies (20), its Cronbach's α coefficient was rather low (0.63) in the present study.

Procedure

The whole procedure was approved by the Ethical Committee of the Faculty of Education and Psychology, Eötvös Loránd University, Hungary. The procedure met the requirements of the World Medical Association Declaration of Helsinki and the Decree No 23/2002 (V. 09.) EüM on Medical Trials Made on Human Subjects. Participants were asked to avoid caffeine intake 12 hours before the experiment. Upon arrival, participants received detailed information about the experimental procedure and signed the informed consent form. Following the placement of ECG-electrodes and the completion of T1 (baseline) measurements (personal data, actual and expected SRQ, SSAS, cardiovascular data, and reaction time), they were arranged in five groups in a quasi-random manner to maintain gender ratio. One group (*natural history group*, $N = 22$) had to drink a cup of room-temperature (approx. 22–23 ºC) water with the instruction that it contains no caffeine (stimulus expectancy in this group was 0.0). The remaining four groups drunk a cup of decaffeinated warm (approx. 40–45 ºC) coffee containing 5 mg/kg caffeine or no caffeine. Two groups (*conditional caffeine group*, $N = 20$ and *conditional placebo group*, $N = 18$) were told that they would drink caffeinated or decaffeinated coffee with equal chance (stimulus expectancy = 0.5) and they received caffeinated or caffeine-free coffee, respectively. The last two groups (*caffeine group*, $N = 25$ and *deceived placebo group*, $N = 22$) were informed that they would receive a cup of strong coffee (stimulus expectancy = 1.0) but they received caffeinated or decaffeinated coffee, respectively. Drinks were serviced by an assistant in a separate room thus the experimenter was not aware of the participants' group affiliation in the remaining part of the experiment. Following the ingestion of the drink, participants were asked to relax for 35 minutes, then they had to rate the perceived strength of the coffee they consumed on a 5-point Likert-scale. Post-experimental analysis revealed that nobody in the deceived caffeine group or in the caffeine group thought that he or she received decaffeinated coffee, thus the deception was considered successful. Finally, T2 data (actual SRQ, cardiovascular data, and reaction time) were recorded, and participants were informed about their group affiliation.

Statistical analysis

Descriptive statistics of the assessed variables were presented in Table I. As we intended to investigate the contribution of multiple factors (e.g. respective baseline value, habitual caffeine consumption, various forms of expectancies, etc.) to the results at T2 and data were appropriate for parametric analysis, multiple linear regression analysis was used. Eight multiple linear regression analyses were carried out with SBP, DBP, HR, HRV (SDNN, HF, LF/HF), reaction time, and SRQ values at T2 as dependent variables, respectively. In each analysis, stimulus expectancies (told likelihood of caffeine intake), actual caffeine intake (0 = no, 1 = yes), habitual caffeine consumption, response expectancies (expected SRQ score), and the respective baseline (T1) value were used as independent (predictor) variables. Variables were entered in one step using the ENTER method.

To explore factors influencing subjective experience, a further analysis with T2 SRQ score as dependent variable was carried out. In the first step of this analysis, changes in

autonomic variables between T1 and T2 (ΔSBP, ΔHR), actual caffeine intake, and baseline SRQ score were entered. In the second step, stimulus and response expectancies, and somatosensory amplification score were stepped in the equation.

Table I. Descriptive statistics (means and SDs) of the assessed variables in the five groups

	Group 1 (control)	Group 2 (conditional placebo)	Group 3 (conditional caffeine)	Group 4 (deceived placebo)	Group 5 (caffeine)
N	**22**	**18**	**20**	**22**	**25**
Habitual caffeine consumption	2.59 ± 1.33	2.83 ± 1.65	2.15 ± 1.03	3.36 ± 1.46	3.76 ± 1.12
Response expectancies	27.13 ± 6.69	26.94 ± 5.36	26.70 ± 5.23	28.18 ± 5.43	31.04 ± 5.20
SSAS	30.72 ± 6.52	28.38 ± 7.57	32.05 ± 4.19	29.72 ± 5.98	31.36 ± 5.34
SBP at T1	122.40 ± 13.44	113.77 ± 10.46	115.90 ± 11.92	124.59 ± 11.32	121.92 ± 13.79
SBP at T2	116.86 ± 12.13	114.72 ± 9.91	121.90 ± 11.96	123.05 ± 10.29	122.08 ± 16.81
DBP at T1	73.22 ± 10.88	70.61 ± 7.66	69.10 ± 6.36	74.04 ± 9.90	69.92 ± 9.09
DBP at T2	73.09 ± 8.28	70.05 ± 7.01	72.10 ± 6.75	73.85 ± 9.94	72.08 ± 12.85
HR at T1	77.05 ± 14.11	73.83 ± 11.96	73.90 ± 10.09	76.72 ± 11.60	79.16 ± 13.77
HR at T2	72.75 ± 12.51	69.22 ± 7.49	66.50 ± 8.04	74.54 ± 15.47	69.20 ± 12.13
HRV-SDNN at T1	213.05 ± 25.46	213.77 ± 17.88	213.20 ± 14.70	212.59 ± 19.00	208.75 ± 20.07
HRV-SDNN at T2	219.50 ± 26.60	220.27 ± 12.65	225.55 ± 14.84	216.68 ± 17.60	221.64 ± 19.77
HRV-HF at T1	24.15 ± 7.37	20.27 ± 7.33	22.55 ± 6.96	21.81 ± 8.39	22.25 ± 7.18
HRV-HF at T2	25.45 ± 8.98	20.22 ± 6.55	21.55 ± 5.72	23.86 ± 11.84	19.64 ± 5.23
HRV-LF/HF at T1	0.54 ± 0.36	0.50 ± 0.44	0.48 ± 0.48	0.45 ± 0.37	0.50 ± 0.27
HRV-LF/HF at T2	0.46 ± 0.27	0.38 ± 0.36	0.29 ± 0.14	0.47 ± 0.29	0.50 ± 0.29
RT at T1	352.70 ± 43.57	359.10 ± 40.24	350.94 ± 29.94	381.93 ± 59.87	361.41 ± 57.40
RT at T2	335.25 ± 42.17	326.05 ± 24.35	332.49 ± 29.92	358.03 ± 51.58	336.38 ± 54.24
SRQ at T1	13.63 ± 4.91	14.16 ± 4.85	14.90 ± 4.33	15.90 ± 5.45	11.84 ± 3.54
SRQ at T2	13.40 ± 4.39	14.33 ± 5.73	15.55 ± 5.44	15.68 ± 4.62	16.40 ± 5.50

Results

Descriptive statistics of the assessed variables were presented in Table I, and results of the eight multiple regression analyses were presented in Table II. In summary, the equation was not significant in the case of LF/HF. Beyond respective baseline (T1) values, actual caffeine intake was a significant predictor of T2 values of SBP, HR (decrease), SDNN, and SRQ. Actual caffeine intake had no impact on values of DBP, HF, and RT at T2. Habitual caffeine consumption and stimulus expectancies (told likelihood of caffeine intake) did not influence any variables at T2. Response expectancy score (expected effects of caffeine) was a significant predictor of SRQ score at T2. It had no impact, however, on any objective variables.

As for the regression analysis exploring factors behind subjective experience, the impact of baseline SRQ score ($\beta = 0.461$; $p < 0.001$) and actual caffeine intake ($\beta = 0.272$; $p < 0.01$) was significant ($R^2 = 0.253$) in the first equation. In the final equation, both of these variables remained significant ($\beta = 0.477$; $p < 0.001$, and $\beta = 0.202$; $p < 0.05$, respectively) and response expectancy score also reached the significance level ($\beta = 0.264$; $p < 0.01$) ($R^2 = 0.334$).

Table II. Results of multiple linear regression analyses

Variable at T2	Significant predictors	Not significant predictors
SBP ($R^2 = 0.471$)	SBP at T1 ($\beta = 0.663$; $p < 0.001$) actual caffeine intake ($\beta = 0.134$; $p < 0.1$)	habitual caffeine consumption told likelihood of caffeine intake expected subjective effects
DBP ($R^2 = 0.349$)	DBP at T1 ($\beta = 0.602$; $p < 0.001$)	actual caffeine intake habitual caffeine consumption told likelihood of caffeine intake expected subjective effects
HR ($R^2 = 0.672$)	HR at T1 ($\beta = 0.798$; $p < 0.001$) actual caffeine intake ($\beta = –0.210$; $p < 0.001$)	habitual caffeine consumption told likelihood of caffeine intake expected subjective effects
SDNN ($R^2 = 0.707$)	SDNN at T1 ($\beta = 0.831$; $p < 0.001$) actual caffeine intake ($\beta = 0.175$; $p < 0.01$)	habitual caffeine consumption told likelihood of caffeine intake expected subjective effects
HF ($R^2 = 0.119$)	HF at T1 ($\beta = 0.348$; $p < 0.001$)	actual caffeine intake habitual caffeine consumption told likelihood of caffeine intake expected subjective effects
LF/HF	–	LF/HF at T1 actual caffeine intake habitual caffeine consumption told likelihood of caffeine intake expected subjective effects
RT ($R^2 = 0.673$)	RT at T1 ($\beta = 0.830$; $p < 0.001$)	actual caffeine intake habitual caffeine consumption told likelihood of caffeine intake expected subjective effects
SRQ ($R^2 = 0.338$)	SRQ at T1 ($\beta = 0.489$; $p < 0.001$) expected subjective effects ($\beta = 0.271$; $p < 0.01$) actual caffeine intake ($\beta = 0.155$; $p < 0.1$)	habitual caffeine consumption told likelihood of caffeine intake

Discussion

In a double-blind, placebo-controlled experiment with a natural history group, consumption of 5 mg/kg caffeine had an impact on participants' SBP, HRV-SDNN, HR (decrease), and subjective experience 40 minutes later even after controlling for respective baseline values, stimulus and response expectancies, and habitual caffeine consumption. No effects on DBP, HRV-HF, HRV-LF/HF, and reaction time were found. Stimulus expectancies (i.e. known chance of receiving caffeine) had no impact on any assessed variable. Beyond actual caffeine intake, response expectancy score was also a determinant of subjective experience which refers to a placebo component in the total effect. Actual autonomic (SBP, HR) changes and somatosensory amplification tendency, however, had no significant impact on subjective experience.

Intake of 5 mg/kg caffeine elevated participants' SBP, decreased their HR, and had not influenced DBP in the current study. As caffeine had an impact on HRV-SDNN which reflects all cyclic components responsible for HR variability and had no impact on the more specific

HF and LF/HF indices, no conclusions can be drawn regarding the autonomic background of this change. Although the hypertensive effect of caffeine is generally accepted (6, 11, 12, 17, 22, 24, 35), it was not demonstrated in all studies (17, 37). HR-related results are also mixed. While no changes following caffeine consumption were detected in some studies (6, 11, 12, 17, 24, 37), a significant decrease in HR was reported in others (22, 35, 40, 49). Reduction of HR possibly reflects a baroreceptor mediated response to pressor action (28). Caffeine-related changes in various indices of HRV were investigated in several placebo-controlled studies with often contradictory results (no data from the caffeine-placebo literature is available, though). Increases in the HF component reflecting parasympathetic (vagal) activity were demonstrated in the majority of the studies (16, 27, 33, 50). No changes in SDNN, HF, and LF/HF were found in two studies (31, 48) and significant decreases were reported in a third paper (41). As for the LF/HF ratio, usually a significant increase has been reported which is attributed to the sympathetic activating effect of caffeine (5, 19, 26). These contradictory results are usually explained by differences in experimental settings and participants' previous experiences with caffeine (2, 23).

Participants' reaction time was not influenced either by caffeine intake or by stimulus expectancies. This finding is in accordance with the results of previous studies (24, 35). In the study of Nash et al. (24), negative results were obtained following the intake of both 125 mg and 325 mg caffeine, and the latter dosage is comparable to that used in the recent study. According to these findings, caffeine may affect vigilance and psychomotor performance but has no direct impact on reaction time.

The only variable in the experiment that was influenced by response expectancies was the SRQ-score, i.e. caffeine related symptoms as experienced by the participants. Although actual caffeine consumption also impacted participants' subjective experience, according to the results of the last regression analysis, this effect could not be tracked down to peripheral autonomic changes (HR and SBP). Consequently, the moderating factor between subjective experience and caffeine intake may have been caffeine's central stimulating effect. Somatosensory amplification tendency did not prove to be a predictor of subjective state either, possibly because it refers to a tendency of amplifying aversive internal states and the SRQ consists of mainly positive items.

Changes in subjective variables are the most often mentioned effects of placebos, in both caffeine-related and medical research. A hypothesis proposed by Benedetti is that the most important mechanism behind objective (autonomic) changes caused by placebos is classical conditioning, while conscious expectations affect mainly subjective variables (4). Although this proposal cannot be regarded as a strict rule, it is in accordance with the majority of placebo-related findings and this is the case in the present study, too.

As for the role of conditional vs. deceptive administration, no significant impact on any outcome measure was found in the current experiment. This negative finding is in accordance with the results of other caffeine studies (24, 46, 47), while differences between the effects of the two administration methods were found in pain-related clinical and experimental placebo studies (30, 43, 44). According to these findings, results obtained from laboratory experiments using caffeine cannot be generalized to medical problems (i.e. external validity of caffeine studies seems to be quite low). Caffeine is mainly used by healthy individuals for recreational purposes and to improve cognitive abilities, and this context is clearly different from illness-related conditions.

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