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ORIGINAL INVESTIGATION

Does coffee enriched with chlorogenic acids improve mood and cognition after acute administration in healthy elderly? A pilot study

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Abstract
Rationale Caffeine exerts positive effects on cognitive and behavioral processes, especially in sub-optimal conditions when arousal is low. Apart from caffeine, coffee contains other compounds including the phenolic compounds ferulic acid, caffeic acid, and the chlorogenic acids, which have purported antioxidant properties. The chlorogenic acids are the most abundant family of compounds found in coffee, yet their effects on cognition and mood have not been investigated.
Objectives This study aims to ascertain whether a coffee rich in chlorogenic acid modulates brain function.
Methods The present pilot study examined the acute effects of decaffeinated coffee with regular chlorogenic acid content and decaffeinated coffee with high chlorogenic acid content on mood and cognitive processes, as measured by behavioral tasks and event-related potentials (ERPs). Performance and ERP responses to a battery of cognitive tasks were recorded at baseline and following the equivalent of three cups of coffee in a randomized, double-blind, crossover study of 39 healthy older participants.
Results Compared with the decaffeinated coffee with regular chlorogenic acid and placebo, caffeinated coffee showed a robust positive effect on higher-level mood and attention processes. To a lesser extent, the decaffeinated coffee high in chlorogenic acid also improved some mood and behavioral measures, relative to regular decaffeinated coffee.
Conclusions Our pilot results suggest that non-caffeine compounds in coffee such as the chlorogenic acids may be capable of exerting some acute behavioral effects, thus warranting further investigation.

Keywords Coffee · Chlorogenic acid · Caffeine · Cognition · Mood · Event-related potentials

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Introduction

Coffee is one of the most popular beverages worldwide (Wang and Ho 2009). Most lauded for its caffeine content, coffee is generally known for its stimulatory effects on behavior. In experimental studies, the most common effects of caffeine are increased alertness, reduced fatigue, and improvements in measures of reaction time, vigilance, and tasks requiring a sustained response (Smith 2002). Previous coffee research has primarily focused on the effects of caffeine on cognition. However, coffee is not only a source of caffeine but is also rich in many bioactive components, including polyphenols such as chlorogenic acids (CGA), caffeic acid, and ferulic acid, which are known to exert

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antioxidant actions (Nardini et al. 2002; Natella et al. 2002; Olthof et al. 2001; Pellegrini et al. 2003).

Despite the worldwide consumption of coffee, the neurophysiological and potential health effects of non-caffeine coffee compounds are poorly understood. Recently, increasing attention has been directed to CGA (the ester of caffeic acid with quinic acid), given its high abundance in coffee, its antioxidant activity (Gomez-Ruiz et al. 2007; Zang et al. 2003), and the suggestion that CGA and/or its metabolites are bioavailable in brain tissue (de Paulis et al. 2002). CGA and its derivatives have displayed antioxidant and neuroprotective properties in models of neurodegenerative and pathological disease (Chu et al. 2009; Han et al. 2010; Hur et al. 2001; Kim et al. 2005; Silva et al. 2004). In addition, there are reports of behavioral effects of CGA including the demonstration that CGA and/or its derivatives reduce anxiety-related behavior (Bouayed et al. 2007), improve spatial learning and memory (Han et al. 2010), and reduce behavioral deficits (Lapchak 2007) in a variety of in vivo animal models of disease or behavior.

Hitherto, the effects of CGA on human cognition and mood are not known. Given emerging evidence indicating neuro-protective and neuro-modulatory effects of CGA in animal models, both in vitro and in vivo, as well as a role for dietary polyphenols in combating against neurodegenerative disease and aging (Esposito et al. 2002; Ramassamy 2006), coffee compounds such as CGA may have a significant health benefit. To explore this issue, the current study examined the acute effect of decaffeinated coffee with high and regular total CGA content in healthy, older volunteers. Caffeinated coffee containing 167 mg caffeine was selected as a positive control, as caffeine at such doses has consistently led to behavioral effects (Smith 2002).

Because there has been little examination of decaffeinated coffee on cognition, the battery of tasks were selected on the basis of previous studies with coffee, as well as those that are sensitive to aging and that differentially reflect higher-level and lower-level cognitive/brain processes. Although the majority of caffeine studies have employed behavioral or performance-based tasks, these are easily influenced by other higher-order processes such as attention, arousal, or motivation, which can modulate the caffeine effect. Electrophysiological event-related potentials (ERPs), which allow measurement of the brain's early responses to the processing associated with cognitive tasks, were thus employed to more easily detect any subtle and discreet effects of caffeine or other coffee compounds on early sensory and perceptual processing. The Rapid Visual Information Processing (RVIP) task was administered given the robust positive effects of caffeine on sustained attention, including the RVIP (Haskell et al. 2008; Smit and Rogers 2000; Warburton 1995; Yeomans et al. 2002), as well as the extensive use of the RVIP to examine the cognitive effects of psychotropic drugs. Further measures included ERP indices of more automatic attention processes (distinct from directed attention) and the negative bias associated with emotional face processing (Huang and Luo 2006; Kerestes et al. 2009), behavioral tasks that show decline with increasing age (e.g., Inspection Time task, Stroop task), and self-report mood and arousal states. Such an extensive range of tasks allowed the cognitive and mood profiles of decaffeinated coffee constituents to be determined.

Because previous studies have suggested that the behavioral effects of caffeine may be moderated by caffeine consumption history (e.g., Haskell et al. 2005), the current study tested only low users of caffeine. Age also appears to be a moderating factor, with older individuals showing greater effects of caffeine on performance than younger individuals (Van Boxtel and Schmitt 2004). Given the apparent sensitivity of older individuals to the effects of caffeine and the emerging role for polyphenols in promoting healthy cognitive aging (Ramassamy 2006), we assessed the behavioral effects of decaffeinated coffee high and regular in CGA and caffeinated coffee in a healthy elderly population. We predicted that the decaffeinated coffee with high CGA content would exert positive effects on mood and cognition relative to the regular CGA decaffeinated coffee.

Materials and methods

Participants

Thirty-nine healthy older volunteers (53–79 years, M=62.5, SD=6.0, 20 male) participated in the study. Inclusion criteria stated that participants were to be relatively light coffee drinkers, drinking typically no more than eight cups of coffee per week (M=6, range=1−8 coffee/week). According to the exclusion criteria, participants were non-smokers and reported to be free of the following: hearing impairment; regular use of psychotropic medication (with the exception of vitamin supplements); allergy to lactose, gluten, or wheat; history of significant neurological, psychiatric, cardiac, endocrine, gastrointestinal, or bleeding disorders; history of substance abuse; and clinically high blood pressure without treatment. Participants were also excluded if they scored<24 on the Mini-Mental State Examination (Folstein et al. 1975). The study was carried out in accordance with the Declaration of Helsinki under the approval of the Human Research Ethics Committee, Swinburne University of Technology, and was registered on the Australian and New Zealand Clinical Trials Registry (ACTRN12609001002279). Written informed consent was obtained from all participants.

Procedure

A double-blind, placebo-controlled crossover design was employed. Each participant was tested under four acute treatments which contained differing amounts of CGA, each separated by at least a 1-week washout period: (1) 6 g of a soluble decaffeinated coffee product containing regular total CGA (224 mg total CGA and 5 mg caffeine; 'Regular CGA Decaf'), (2) 6 g of a specially processed soluble decaffeinated coffee co-extracted from roasted and green beans with high total CGA (521 mg total CGA and 11 mg caffeine; 'High CGA Decaf'), (3) 6 g of a soluble caffeinated coffee containing moderate–high total caffeine and regular total CGA (244 mg total CGA and 167 mg caffeine; 'Caffeinated Coffee') and (4) 6 g of placebo, made of maltodextrin mixed with coffee flavor and color (0 mg total CGA and 0 mg caffeine; 'Placebo'). Refer to Table 1 for detailed coffee composition. Note that 6 g of soluble coffee is equivalent to three standard servings. Testing sessions commenced either in the morning or afternoon (counterbalanced between participants), which remained constant for each participant across sessions.

Participants attended a training session to familiarize themselves with the task procedures and to confirm eligibility. On treatment days, participants were instructed to abstain from alcohol and foods and beverages containing caffeine, chlorogenic acids, and high polyphenol content for 24 h before each session. Upon arrival at the Institute, participants were prepared for electrophysiological recording. They then completed baseline cognitive testing and EEG recording, which lasted approximately 70 min. Following baseline testing, participants consumed the equivalent of three cups of soluble coffee (6 g dissolved in 300 ml of hot water), with whole milk and saccharin added if the participant desired. In a previous pharmacokinetic study, it was found that adding whole milk to instant coffee does not alter the overall bioavailability of coffee phenolic acids (Renouf et al. 2010b). Post-coffee testing was performed 40 min following coffee consumption, which coincided with approximate peak CGA blood concentrations (Renouf et al. 2010a).

Electrophysiological data acquisition

EEG was recorded with Neuroscan 4.3.1 acquisition software and a Synamps2 amplifier from 64 tin scalp electrodes (using a Quickcap) according to the international 10–20 system. Five additional electrodes were added: two placed above and below the left eye and two placed at the outer canthus of each eye for recording eye movement activity (electro-oculogram, EOG), and one placed at the tip of the nose. Online, EEG data were referenced to the point midway between Cz and CPz and grounded midway between Fz and FPz. EEG data were collected with a sampling rate of 500 Hz, a gain of 2816 and a lowpass filter of 70 Hz.

Neuropsychological assessment

A battery of cognitive, mood, and ERP tasks were performed in a fixed order. These tasks, and their outcome measures, are described in Table 2. For widely used

Table 1 Composition of the study coffee treatments per serving

Coffee compound	Regular CGA decaf	High CGA decaf	Caffeinated coffee	Placebo
CGA and its derivatives (mg)				
3-CQA	41.4	108	43.8	0
4-CQA	44.4	109.8	49.2	0
5-CQA	75.6	177	84	0
Sum CQAs	161.4	394.8	177	0
3-fqa	9.6	4.8	9	0
4-fqa	12	23.4	12.6	0
5-fqa	11.4	28.8	13.2	0
sum FQAs	33.6	57.6	34.8	0
3,4-diCQA	3	18.6	4.2	0
3,5-diCQA	1.8	12	2.4	0
4,5-diCQA	3	18.6	4.2	0
sum diCQAs	7.8	49.2	10.2	0
CQA lactones	21	19.2	22.2	0
Total CGAs (mg)	223.8	520.98	244.26	0
Caffeic acid (mg)	1.2	2.4	1.8	0
Ferulic acid (mg)	0.12	0.18	0.18	0
Caffeine (mg)	4.8	11.4	167.4	0

CQA caffeoylquinic acid, *FQA* feruloylquinic acid, *diCQA* dicaffeoylquinic acid, *CGA* chlorogenic acids

Table 2 Neuropsychological test battery

Test	Cognitive domain	Outcome measure	Reference
Bond and Lader Visual Analogue Scales (VAS) (Bond and Lader 1974)	Self-report mood	Alertness, calmness, and contentedness mood factors	Bond and Lader (1974)
Caffeine Research Visual Analogue Scales (CRVAS)	Self-report mood	Relaxed, alert, jittery, tired, tense, headache, overall mood, mentally fatigued scales	Haskell et al (2005); Rogers et al (2003)
Visual Verbal Learning Test (VVLT) immediate verbal recall (three trials)	Short-term memory	Maximum number of correctly recalled words (%) in any three trials	Evers et al (2005)
Rapid Visual Information Processing (RVIP)	Sustained attention	Accuracy, mean RT, false alarms, P300, CNV	Gilbert et al (2007); Jones et al (1992)
Mismatch negativity (MMN)	Pre-attentive functioning, auditory discrimination	MMN mismatch waveform[a]	Leung et al (2008); Näätänen, (1992)
VVLT verbal delayed recall	Retrieval from long-term memory	Number of correctly recalled words (%)	Evers et al (2005)
VVLT delayed recognition	Storage in long-term memory	Reaction time and accuracy of original words as percentages	
Emotional face recognition task (EFRT)	Emotional processing	N170, N250, and accuracy negative bias[b]	Labuschagne et al (2010)
Inspection time (IT)	Perceptual speed	IT (ms)	Nathan et al (2004)
Stroop Color-Word Test (SCWT) (Hammes 1973)	Cognitive flexibility, susceptibility to cognitive interference	Stroop interference[c]	Van der Elst et al (2006)

Tasks are listed in order of presentation. The cited references provide a basic description of the task.

RT reaction time, *CNV* contingent negative variation

[a] Generated by a "mismatch" process between the auditory input from the deviant stimulus with the auditory memory of the standard stimulus

[b] Negative emotional bias represents the tendency to preferentially process negative emotional stimuli. We defined negative bias as the difference between happy and sad values

[c] SCWT interference represents the extra time needed to complete subtest III, relative to the average of subtest I and II (interference=time subtest III−(time subtest I+time subtest II)/2)

behavioral tasks, please refer to the cited reference for a full description of the test. ERP tasks and their analysis are described below. At each assessment period, alternate test versions were used. All tasks (where applicable) were preceded by a brief practice. Stimuli for ERP tasks and the visual verbal learning task were presented using NeuroScan STIM2 hardware and software (NeuroScan Labs, Virginia, USA).

ERP tasks and analysis

EEG data were visually inspected and segments removed where artifactual, re-referenced to digitally linked mastoids, lowpass filtered at 30 Hz (12 dB/oct), epoched, baseline-corrected, and corrected for ocular artifact using the Croft and Barry (2000) method. For the MMN task, EEG data were also re-referenced to the nose, bandpass filtered (1–30 Hz, 12 dB/oct) but were not EOG-corrected. Trials with excessive artifacts (i.e., EEG>±75 μV) were rejected, with the remaining data averaged for each stimulus-type separately. Grand means across all sessions and subjects were created for task-specific ERP waveforms to aid in the determination of the ERP peaks and/or mean area under the curve (AUC) measure. Subsequently, for each individual and session, the peak or AUC was automatically extracted for each ERP task, treatment (Regular CGA Decaf, High CGA Decaf, Caffeinated Coffee, Placebo) and phase (baseline and post) from the individuals' averages.

Rapid visual information processing Participants monitored a continuous series of digits (1–9) for targets (three consecutive odd or even digits in ascending order), pressing the 'yes' response button as soon as a target string was detected. Digits were presented at the rate of 100 min^{-1} for 12 min, with eight correct target strings presented each minute. Outcome measures were the percentage of targets correctly detected 200–1,200 ms post target (accuracy), mean reaction time for correct detections, false alarm rate (FAR), and two ERP components reflecting attentional processes: the P300 amplitude (or specifically the P3b, see Polich 2007) in response to target strings (indexing attention to targets) and the contingent negative variation (CNV), a slow, negative-going voltage potential indexing anticipation of these target strings (Gilbert et al. 2007).

For the P300, data were epoched −100 to 600 ms post-target digit and baseline-corrected −100 to 0 ms. The P300 was defined as the mean AUC 280–480 ms post-target digit at the Pz electrode. P300 ERPs were omitted if they comprised less than 30 "clean" epochs following data analysis. For the CNV, data were epoched −1,300 to 600 ms post-target digit and baseline-corrected −1,000 to −900 ms. Two CNV components were assessed at the Fz electrode: the CNV1 which was defined as the mean AUC −700 to −600 ms post-target digit (i.e., the mean amplitude from 100 ms before the pre-target digit to the onset of the pre-target digit) and the CNV2 which was defined as the mean AUC −100 to 0 ms post-target digit (i.e., the mean amplitude from 100 ms before the target digit to the onset of the target digit). To quantify the increase in voltage negativity due to anticipation of a target string, CNV1 was subtracted from CNV2. If a participant's final average comprised ten or less, "clean" epochs following data analysis, this was omitted from further analysis.

Mismatch negativity The auditory MMN is an early ERP component that provides a sensitive index of the brain's pre-attentive auditory change detection system (Näätänen 1992) and was performed to assess early, more-automatic attentional function. We employed a duration MMN paradigm, where stimuli were 890, 80 dB sound pressure level, and 1,000 Hz tones presented binaurally via headphones with a mean stimulus onset asynchrony (SOA) of 300 ms (range, 250–350 ms). Ninety-one percent of tones were 50 ms (standards), and 9% were 100 ms (deviants) duration (including 10-ms rise/fall times). Participants were instructed to rest with their eyes open throughout the task.

EEG data were epoched −100–250 ms post-stimulus (discarding the first eight stimuli to reduce novelty effects). Standards (excluding post-deviant standards) and deviants were averaged separately, and mismatch waveforms were subsequently obtained by subtracting the standard from the deviant averaged waveform. The Grand Mean MMN waveform (re-referenced to the nose) met the constraint of showing frontal topography and a prominent polarity reversal at Fz relative to the digitally linked mastoids (i.e., temporal bone). Individual MMN waveforms were then re-referenced to the mastoids. Based on the time range of the mastoid reversals, the MMN waveform was defined as the mean AUC 110–210 post-stimulus at the Fz electrode. Electrophysiological data were omitted if they were comprised of fewer than 30 clean epochs following data analysis.

Emotion face recognition task An emotional face recognition ERP paradigm was performed to provide a sensitive and objective measure of early emotional processing, with a specific focus on negative emotional bias. We have recently shown that this face recognition ERP paradigm is sensitive to acute pharmacological treatment (selective serotonin reuptake inhibitors), switching attentional bias from negative towards positive emotional stimuli (Kerestes et al. 2009). As per Labuschagne et al (2010), happy, sad, and neutral faces were presented on a computer screen and participants were required to identify the emotion by pressing a corresponding button as quickly and accurately as possible. Face stimuli taken from the Ekman Pictures of Affect Series (Ekman and Friesen 1976) consisted of six actors (three males), with each emotion presented 108 times (18 times by each actor). Each trial began with a fixation cross for 300 ms, followed by the face (with "happy", "neutral", "sad" labels on the bottom of the screen as a reminder of the corresponding buttons) for 1,200 ms. Mean SOA was 1,500 ms (range, 1,300–1,700 ms). Percent correct recognition (accuracy) 100–1,300 ms post-stimulus was calculated. Outcome measures were the negative bias indices (i.e., the difference between responses to sad and happy stimuli; NBI), for each of Accuracy, and the N170 (reflecting structural encoding; Eimer and Holmes 2007) and N250 (reflecting specific emotion processing; Streit et al. 2000) ERP peaks.

EEG data were epoched −200 to 1,000 ms post-stimulus presentation and averages created separately for each emotion type. Based on the Grand Mean waveform (combining participant, condition, and emotion), the N170 component was defined as the negative peak 138–198 ms post-stimulus and the N250 as the negative peak 260–380 ms post-stimulus (from the average of electrodes P07 and P08). An index of 'negative bias' was subsequently calculated for N170 and N250 waveforms by subtracting the happy face peak amplitude value from the sad face peak amplitude value (i.e., the difference in magnitude of the sad and happy ERP peak values). ERPs were omitted if they comprised less than 30 clean epochs following data analysis.

Statistical analysis

For all tasks, difference scores were calculated by subtracting the baseline score from the corresponding experimental score. Parametric (or the non-parametric equivalent where data was not normally distributed and could not be transformed) statistical analyses were performed to determine treatment effects, with the ERP or behavioral measure the dependent variable. A preliminary analysis consisted of a planned comparison testing for the effect of Caffeinated Coffee against Placebo (to examine the effect of coffee as a "positive control"), for each of the dependent variables. Experimental analyses were planned comparisons testing for the effect of High CGA Decaf compared with Regular CGA Decaf (to examine the effect of CGAs) and Caffeinated Coffee compared with Regular CGA Decaf (to examine the effect of caffeine), with an alpha level of 0.05. To allow

greater exploration of the data, p values <0.100 were taken as trend-level.

Results

Participant data omitted from the planned comparisons due to insufficient epoch number, erroneous (non-biological) values, or missing data are reflected in the degrees of freedom in the each analysis. Statistical analyses are assumed to be parametric (repeated-measures t tests), unless non-parametric (Wilcoxon's Signed Rank) tests are stipulated below, and only results at $p<0.10$ are described. Table 3 presents the mean and standard deviation (SD) values for each measure, for each treatment condition, for each of the baseline, treatment, and difference scores separately.

Rapid visual information processing

Preliminary Non-parametric tests were conducted separately for each of the five RVIP dependent measures (% Accuracy, RT, FAR, P300, CNV). Confirming that the experimental manipulation was achieved, Caffeinated Coffee improved RVIP accuracy relative to Placebo (Z[39]=3.03, $p<0.001$), such that, while there was a slight decrease in accuracy associated with Placebo, accuracy significantly increased with Caffeinated Coffee. No other treatment effects were observed.

Experimental Confirming an effect of caffeine, Caffeinated Coffee improved RVIP accuracy relative to Regular CGA Decaf (Z[39]=2.09, $p=0.037$). No other treatment effects were observed.

Mismatch negativity

Preliminary No effects of Caffeinated Coffee relative to Placebo were found on MMN amplitude.

Experimental No differences were found between High CGA Decaf and Regular CGA Decaf, or between Caffeinated Coffee and Regular CGA Decaf.

Face recognition task (emotional negative bias)

Preliminary Relative to Placebo, no effects of Caffeinated Coffee were found on $NBI_{accuracy}$, NBI_{N170} (non-parametric), or NBI_{N250}.

Experimental High CGA Decaf reduced $NBI_{accuracy}$ relative to Regular CGA Decaf (F[1,38]=6.08, $p=0.018$, $\eta p2=0.14$; Fig. 1). No effect of High CGA Decaf was found on NBI_{N250} or NBI_{N170} (non-parametric) relative to Regular CGA Decaf. No differences were found between Caffeinated Coffee and Regular CGA Decaf on any of the emotional negative bias measures.

Visual verbal learning test

Preliminary Caffeinated Coffee impaired delayed recall relative to Placebo (F[1,38]=5.76, $p=0.021$, $\eta p2=0.13$). No preliminary effects were observed on immediate recall or delayed recognition (non-parametric).

Experimental Caffeinated Coffee tended to impair delayed recall relative to Regular CGA Decaf (F[1,38]=3.04, $p=0.089$, $\eta p2=0.07$). No other experimental effects were observed on immediate recall, delayed recall, or delayed recognition (non-parametric).

Inspection time

Preliminary There was no effect of Caffeinated Coffee compared with Placebo on Inspection Time (IT) (non-parametric).

Experimental High CGA Decaf resulted in a trend-level slowing of IT from the baseline to the experimental condition, compared with Regular CGA Decaf (Z[36]=1.65, $p=0.099$). No other experimental analyses were significant (non-parametric).

Stroop color–word test—interference

Preliminary Compared with Placebo, there was no effect of Caffeinated Coffee on SCWT Interference (non-parametric).

Experimental Relative to Regular CGA Decaf, there was no effect of High CGA Decaf or Caffeinated Coffee on SCWT Interference (non-parametric).

VAMS (mood)

Preliminary Caffeinated Coffee increased "Alertness" and "Content" scores relative to Placebo (Z[37]=2.04, $p=0.013$, and Z[39]=1.65, $p=0.032$, respectively). No other effects were found (all analyses non-parametric).

Experimental High CGA Decaf increased "Alertness" relative to Regular CGA Decaf (Z[38]=2.98, $p=0.003$; Fig. 2). Caffeinated Coffee also increased "Alertness" and "Content" scores relative to Regular CGA Decaf (Z[38]=3.33, $p=0.001$ and Z[39]=1.83, $p=0.067$, trend-level, respectively). No other experimental effects were found (all analyses non-parametric).

Table 3 Means (and SD) for each of the cognitive endpoints, within each treatment and phase separately

Cognitive endpoints	Treatment	*N*	Phase		
			Pre	Post	Diff
RVIP RT	High CGA Decaf	39	412.1 (66.9)	416.6 (78.3)	4.5 (43.6)
	Regular CGA Decaf	39	418.8 (77.3)	411.3 (72.3)	−7.4 (39.7)
	Caffeinated coffee	39	410.2 (69.7)	398.0 (67.0)	−12.2 (31.7)
	Placebo	39	427.8 (97.6)	420.3 (81.6)	−7.5 (49.9)
RVIP Accuracy (%)	High CGA	39	65.4 (19.1)	66.2 (19.4)	0.9 (10.0)
	Regular CGA	39	67.1 (19.1)	67.7 (19.5)	0.7 (7.3)
	Caffeinated coffee*****[a]; **[b]	39	65.4 (20.5)	69.5 (18.9)	4.2 (9.5)
	Placebo	39	66.4 (20.7)	64.4 (21.0)	−2.0 (9.8)
RVIP False Alarm Rate (RVIP FAR)	High CGA Decaf	39	0.5 (1.1)	0.5 (0.9)	−0.1 (0.8)
	Regular CGA Decaf	39	0.5 (0.8)	0.4 (0.7)	−0.1 (0.3)
	Caffeinated coffee	39	0.5 (0.8)	0.4 (0.8)	−0.1 (0.4)
	Placebo	39	0.6 (1.4)	0.5 (1.0)	−0.2 (0.5)
RVIP P300	High CGA Decaf	35	2.72 (2.85)	2.54 (2.05)	−0.18 (2.11)
	Regular CGA Decaf	38	2.73 (3.59)	2.32 (2.89)	−0.41 (3.05)
	Caffeinated coffee	37	2.54 (2.59)	2.85 (2.56)	0.31 (2.02)
	Placebo	38	2.48 (2.82)	3.07 (2.55)	0.59 (2.59)
RVIP CNV	High CGA Decaf	33	−3.1 (3.4)	−3.1 (2.7)	0.1 (3.3)
	Regular CGA Decaf	36	−3.2 (2.9)	−2.8 (2.4)	0.4 (2.3)
	Caffeinated coffee	37	−2.7 (2.5)	−2.4 (2.5)	0.3 (2.7)
	Placebo	37	−3.4 (3.9)	−3.1 (2.9)	0.4 (3.3)
MMN	High CGA Decaf	31	−2.03 (1.01)	−2.21 (1.16)	−0.18 (1.09)
	Regular CGA Decaf	31	−1.91 (1.13)	−1.85 (0.90)	0.06 (1.26)
	Caffeinated coffee	31	−1.91 (1.06)	−1.9 (1.26)	0.01 (0.82)
	Placebo	31	−1.75 (1.24)	−1.90 (1.11)	−0.15 (1.13)
EFRT N170'Negative bias'(sad – happy)	High CGA Decaf	32	0.08 (0.73)	0.02 (0.76)	−0.06 (1.10)
	Regular CGA Decaf	37	0.01 (0.77)	−0.01 (0.63)	−0.03 (1.01)
	Caffeinated Coffee	36	−0.34 (1.10)	0.13 (0.54)	0.48 (0.95)
	Placebo	34	−0.07 (0.58)	−0.02 (0.99)	0.05 (1.2)
EFRT N250'Negative bias'(sad – happy)	High CGA Decaf	28	0.54 (0.97)	0.55 (0.68)	0.01 (1.09)
	Regular CGA Decaf	28	0.58 (0.75)	0.52 (0.81)	−0.06 (1.10)
	Caffeinated Coffee	28	0.34 (0.80)	0.49 (0.87)	0.14 (1.14)
	Placebo	28	0.23 (0.56)	0.70 (0.85)	0.46 (0.89)
EFRT Accuracy 'Negative bias' (sad – happy)	High CGA Decaf***[b]	39	−27.1 (28.1)	−29.8 (27.0)	−2.7 (16.8)
	Regular CGA Decaf	39	−30.1 (23.3)	−24.9 (28.0)	5.2 (17.3)
	Caffeinated coffee	39	−26.8 (22.2)	−27.4 (26.3)	−0.57 (19.0)
	Placebo	39	−30.1 (22.1)	−30.4 (23.7)	−0.33 (13.25)
VVLT immediate recall (%)	High CGA Decaf	39	76.9 (14.3)	70.8 (14.7)	−6.2 (15.8)
	Regular CGA Decaf	39	78.1 (13.2)	70.6 (17.2)	−7.5 (14.2)
	Caffeinated coffee	39	76.4 (16.2)	69.7 (13.2)	−6.7 (13.5)
	Placebo	39	74.2 (14.8)	68.7 (15.8)	−5.5 (12.9)
VVLT delayed recall (%)	High CGA Decaf	39	53.2 (21.1)	35.9 (21.3)	−17.3 (20.3)
	Regular CGA Decaf	39	55.6 (18.8)	38.1 (22.3)	−17.4 (20.8)
	Caffeinated coffee***[a]; *[b]	39	57.8 (22.5)	32.5 (18.3)	−25.3 (19.3)
	Placebo	39	49.9 (23.5)	35.0 (23.0)	−14.9 (21.8)
VVLT delayed recognition (%)	High CGA Decaf	39	86.7 (18.4)	82.6 (17.8)	−4.1 (22.2)
	Regular CGA Decaf	39	89.2 (11.6)	84.6 (15.8)	−4.6 (15.8)
	Caffeinated Coffee	39	87.0 (13.5)	85.1 (14.0)	−1.9 (15.5)

Table 3 (continued)

Cognitive endpoints	Treatment	*N*	Phase		
			Pre	Post	Diff
	Placebo	39	87.0 (13.9)	79.8 (21.5)	−7.2 (20.1)
Inspection Time	High CGA Decaf*[b]	36	107.8 (34.5)	118.9 (52.5)	11.1 (43.7)
	Regular CGA Decaf	38	128.2 (43.9)	121.8 (55.6)	−6.3 (57.1)
	Caffeinated Coffee	38	112.4 (35.8)	114.8 (36.6)	2.43 (32.3)
	Placebo	37	119.1 (49.5)	120.3 (42.9)	1.15 (40.3)
SCWT-Interference	High CGA Decaf	38	39.8 (12.0)	38.0 (12.6)	−1.9 (8.8)
	Regular CGA Decaf	38	39.3 (13.8)	38.8 (14.1)	−0.45 (10.1)
	Caffeinated Coffee	38	38.9 (11.1)	38.1 (9.2)	−0.77 (7.1)
	Placebo	38	38.5 (11.0)	37.9 (13.5)	−0.61 (6.6)
Bond-Lader Alert	High CGA Decaf****[b]	39	71.45 (18.67)	72.26 (18.23)	0.814 (13.16)
	Regular CGA Decaf	38	75.96 (14.31)	69.52 (18.84)	−6.43 (11.49)
	Caffeinated Coffee***[a]; ****[b]	38	73.17 (18.47)	75.48 (18.48)	2.31 (8.54)
	Placebo	38	72.75 (17.17)	69.52 (19.61)	−3.23 (11.32)
Bond-Lader Calm	High CGA Decaf	39	78.0 (17.75)	71.65 (21.0)	−6.34 (15.73)
	Regular CGA Decaf	39	78.95 (14.03)	75.46 (19.79)	−3.49 (18.53)
	Caffeinated coffee	39	77.78 (15.22)	76.79 (18.18)	−0.99 (10.67)
	Placebo	39	78.29 (16.43)	77.48 (16.78)	−0.812 (10.9)
Bond-Lader Content	High CGA Decaf	39	80.09 (16.35)	78.49 (15.29)	−1.60 (9.9)
	Regular CGA Decaf	39	80.51 (13.03)	78.77 (14.79)	−1.74 (9.6)
	Caffeinated coffee**[a]; *[b]	39	79.11 (16.03)	79.85 (17.15)	0.74 (7.6)
	Placebo	39	80.95 (11.5)	78.42 (15.06)	−2.5 (7.97)
CRVAS Relaxed	High CGA Decaf	38	73.19 (19.75)	74.37 (16.33)	1.18 (14.18)
	Regular CGA Decaf	39	73.61 (15.73)	70.59 (19.87)	−3.02 (19.03)
	Caffeinated Coffee****[a]	38	71.96 (16.82)	76.73 (15.19)	4.77 (10.20)
	Placebo	39	75.05 (17.51)	70.81 (18.13)	−4.25 (13.38)
CRVAS Alert	High CGA Decaf	38	66.28 (24.0)	68.50 (20.58)	2.22 (21.50)
	Regular CGA Decaf	39	70.67 (16.30)	67.98 (20.71)	−2.70 (12.71)
	Caffeinated Coffee***[a]; *[b]	38	67.05 (21.97)	72.31 (19.13)	5.26 (18.37)
	Placebo	39	66.91 (22.13)	62.87 (23.14)	−4.03 (22.93)
CRVAS Jittery	High CGA Decaf	38	16.37 (16.56)	16.39 (16.07)	0.03 (15.05)
	Regular CGA Decaf	39	14.61 (16.02)	19.55 (18.75)	4.94 (16.99)
	Caffeinated coffee	38	18.97 (19.58)	20.78 (23.94)	1.81 (17.68)
	Placebo	39	14.77 (17.93)	15.38 (16.65)	0.61 (15.75)
CRVAS Tired	High CGA Decaf	38	30.40 (22.81)	35.62 (24.05)	5.22 (23.49)
	Regular CGA Decaf	39	27.27 (18.33)	38.70 (25.63)	11.43 (18.43)
	Caffeinated coffee***[a]; **[b]	38	29.99 (23.78)	28.87 (22.34)	−1.12 (25.29)
	Placebo	39	28.37 (20.89)	38.86 (24.83)	10.50 (22.02)
CRVAS Tense	High CGA Decaf	38	18.61 (17.61)	19.90 (17.45)	1.29 (13.44)
	Regular CGA Decaf	39	17.68 (15.08)	22.81 (19.85)	5.13 (18.16)
	Caffeinated coffee**[a]; ***[b]	38	19.05 (16.41)	17.49 (18.47)	−1.56 (15.02)
	Placebo	39	15.52 (14.49)	20.22 (18.50)	4.70 (15.26)
CRVAS Headache	High CGA Decaf*[b]	38	14.47 (27.52)	12.34 (21.02)	−2.14 (31.37)
	Regular CGA Decaf	39	7.99 (12.13)	13.51 (20.99)	5.53 (17.99)
	Caffeinated coffee****[a]; **[b]	38	8.42 (11.61)	7.73 (13.52)	−0.69 (10.7)
	Placebo	39	8.09 (11.48)	14.26 (19.84)	6.17 (18.45)
CRVAS Overall Mood	High CGA Decaf	38	81.77 (15.89)	75.77 (20.08)	−6.00 (16.55)
	Regular CGA Decaf	39	82.69 (11.12)	76.58 (19.13)	−6.12 (16.46)

Table 3 (continued)

Cognitive endpoints	Treatment	*N*	Phase		
			Pre	Post	Diff
	Caffeinated coffee*****[a]; ****[b]	38	72.64 (24.66)	78.84 (20.43)	6.20 (24.2)
	Placebo	39	82.08 (14.01)	77.08 (16.66)	−4.99 (11.47)
CRVAS Mentally Fatigued	High CGA Decaf*[b]	38	32.73 (27.58)	34.13 (24.87)	1.40 (23.49)
	Regular CGA Decaf	39	25.53 (22.27)	34.78 (27.50)	9.24 (24.29)
	Caffeinated coffee*****[a]; ****[b]	38	34.81 (27.30)	28.62 (22.40)	−6.20 (27.15)
	Placebo	39	25.91 (22.64)	39.21 (26.69)	13.30 (22.75)

[a] Indicates significant effect compared with Placebo (positive control comparison)

[b] Indicates significant effect compared with Regular CGA Decaf (experimental comparisons)

*P<0.1; **P<0.05; ***P<0.025; ****P<0.01; *****P<0.001

CRVAS (mood)

Preliminary Relative to Placebo, Caffeinated Coffee increased scores on Items 1 (Relaxed), 2 (Alert), and 7 (Overall Mood), and decreased scores on Items 4 (Tired), 5 (Tense), 6 (Headache), and 8 (Mentally Fatigued) (Z[38]=2.76, p=0.002; Z[38]=2.16, p=0.010; Z[38]=3.70, p<0.001; Z[38]=1.86, p=0.021; Z[38]=1.72, p=0.028; Z[38]=2.33, p=0.007, and Z[38]=3.43, p<0.001, respectively).

Experimental High CGA Decaf showed trend-level decreases on Items 6 (Headaches) and 8 (Mentally Fatigued) relative to Regular CGA Decaf (Z[38]=1.71, p=0.087, trend-level and Z[38]=1.78, p=0.074, trend-level, respectively; Fig. 2). Relative to Regular CGA Decaf, Caffeinated Coffee increased scores on Items 2 (Alert) and 7 (Overall Mood), and decreased scores on Items 4 (Tired), 5 (Tense), 6 (Headache), and 8 (Mentally Fatigued) (Z[38]=1.78, p=0.075, trend-level; Z[38]=2.93, p=0.003; Z[38]=2.06, p=0.04; Z[38]=2.43, p=0.015; Z[38]=2.24, p=0.025; Z[38]=2.60, p=0.009, respectively).

Discussion

The current study investigated the acute effects of high versus regular CGA decaffeinated coffee on a comprehensive battery of mood and high- and low-level cognitive processes in an elderly population. Despite the substantial amount of research examining the behavioral effects of caffeine, to our knowledge, no study has explicitly sought to assess the effects of other coffee compounds on mood and cognition. The pattern of our pilot results suggests that non-caffeine compounds in coffee, such as the chlorogenic acids, are capable of exerting some acute mood and mood-related behavioral changes.

In order to show that our methodology was successful and to provide a context for understanding the effects of the

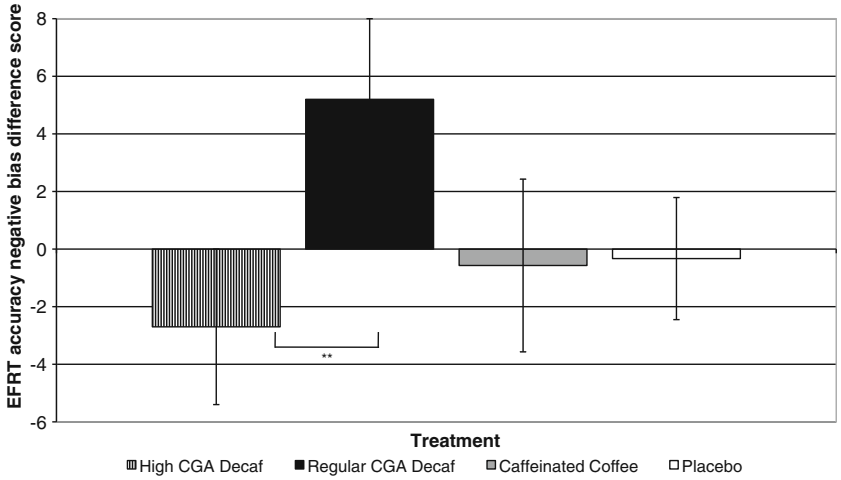

Fig. 1 Mean difference scores (with SEM error bars) of the emotion face recognition task negative bias accuracy index for each treatment condition. **P<0.025

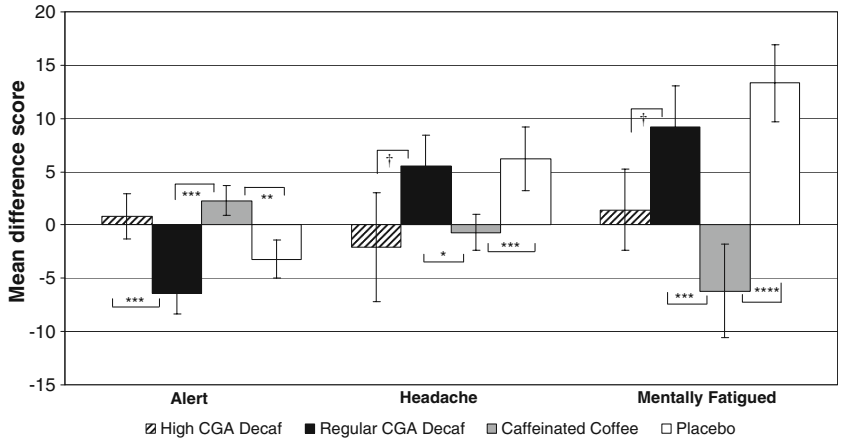

Fig. 2 Mean difference scores (with SEM error bars) of VAMS "Alert" and CRVAS "Headache" and "Mentally Fatigued" mood items, for each treatment condition. †$P<0.1$; *$P<0.05$; **$P<0.025$; ***$P<0.01$; ****$P<0.001$

enriched CGA decaffeinated coffee on human mood and behavior, planned comparisons were performed that tested for an effect of Caffeinated Coffee against Placebo (preliminary) and Regular CGA Decaf (experimental). Caffeinated coffee was selected at a dose that has robustly produced behavioral effects. As expected and consistent with its psychostimulant properties, Caffeinated Coffee showed mood- and attention-enhancing effects relative to both Placebo and Regular CGA Decaf, indicating that (a) our methodology was successful (Caffeinated Coffee against Placebo) and (b) caffeine produced these effects[1] (Caffeinated Coffee against Regular CGA Decaf). Caffeinated Coffee increased self-reports of relaxation, alertness, contentedness and overall mood, and reduced mental fatigue, headache, tiredness, and tension. Corresponding to this, Caffeinated Coffee also improved accuracy on the RVIP sustained attention task. These findings are consistent with numerous reports of caffeine exerting positive effects on mood, sustained attention and vigilance (see Koelega 1993; Smith 2002), and specifically the RVIP (Frewer and Lader 1991; Haskell et al. 2008; Rees et al. 1999; Smit and Rogers 2000; Warburton 1995; Yeomans et al. 2002). Interestingly, delayed recall on the visual verbal learning test (VVLT) was worse following Caffeinated Coffee relative to both Placebo and Regular CGA Decaf. Although this finding may seem counterintuitive, the observation that Caffeinated Coffee showed greater impairment on delayed recall supports the suggestion that the stimulant properties of caffeine facilitates low-, but hinders or does not affect high-memory load tasks (Humphreys and Revelle 1984). The demonstration that Caffeinated Coffee affected the same behavioral measures relative to both Placebo and Regular CGA Decaf, as well as the lack of effect of Caffeinated Coffee on other cognitive and electrophysiological measures, suggests a relative selectivity of caffeine (by itself or in combination with non-caffeine compounds) for higher-level mood and attention processes. Although these findings are not new in themselves, they do demonstrate the sensitivity of the behavioral tasks (and perhaps the lack of sensitivity of our ERP tasks) to acute pharmacological manipulation, in our sample of healthy elderly volunteers.

The effect of non-caffeine constituents in coffee such as chlorogenic acid was investigated via decaffeinated coffee and specifically through comparison of decaffeinated coffees differing in CGA content level (High CGA Decaf against Regular CGA Decaf). Interestingly, our pilot results showed that the experimental decaffeinated coffee with higher total CGA content (High CGA Decaf) exerted some positive effects on mood-related processes. Specifically, it increased alertness and tended to decrease headaches and mental fatigue, relative to Regular CGA Decaf. In some agreement with these self-report mood effects, High CGA Decaf reduced the negative bias accuracy index on the emotional face recognition task relative to Regular CGA Decaf, indicating a modulatory effect of High CGA Decaf on emotional processing bias during higher-order emotional expression decoding, similar to that which has been reported with serotonergic and noradrenergic antidepressants (Kerestes et al. 2009; Labuschagne et al. 2010). Given that CGA content was the compound that markedly differed between High and Regular CGA Decaf, these pilot results suggest that CGAs are capable of exerting distinct mood changes.

To date, there are few data investigating the physiological mechanisms of CGA and particularly the mechanisms underlying its acute CNS effects. It is important to note that our study addressed acute effects only, and as such, our pilot results may be affected by duration of use. Although in vitro effects of CGA implicate antioxidant and neuroprotective mechanisms (Chu et

[1] Note that Caffeinated Coffee increased the CRVAS 'Relaxed' scores relative to Placebo but not Regular CGA Decaf. This may suggest that CGA played a role in this improvement. However, as High did not differ from Regular CGA Decaf on this metric, this argues against CGA playing a role in that finding.

al. 2009; Han et al. 2010; Kono et al. 1998; Zang et al. 2003), these likely confer with long-term use. Recently, acute CGA administration has been reported to have anti-amnesic (Kwon et al. 2010) and anxiolytic (Bouayed et al. 2007) effects in animal models of disease or behavior. The mechanisms underlying the acute behavioral effects of CGA are unknown, although it has been suggested that it may involve activation of benzodiazepine receptors (Bouayed et al. 2007), anti-acetylcholinesterase effects (Kwon et al. 2010) or vascular effects given the action of acute intake of other polyphenols on markers of vascular function (Faridi et al. 2008; Kennedy et al. 2010; Schroeter et al. 2006) which has been suggested to underpin their acute cognitive effects (Scholey et al. 2010). Nevertheless, given the scarcity of available data examining acute CGA effects, the above mechanisms are speculative, requiring further investigation.

There are limitations that warrant discussion. Firstly, a number of statistical comparisons were performed without Bonferroni correction, and trend-level findings were reported. This was done to provide exploration of the data given the pilot nature of the study. Although our study is consequently at risk of false-positive findings, the results represent a consistent pattern and are thus supported by concurrent validity. Nevertheless, these results are exploratory and thus require replication. Secondly, the High CGA Decaf had slightly more caffeine than Regular CGA Decaf, 11 mg as opposed to 5 mg, respectively. It is possible therefore, that the effects of High CGA Decaf were due to the increased caffeine content, as has been reported by Smit and Rogers (2000) with a similar dose (12.5 mg). Nevertheless, this does not appear likely given that Smit and Rogers (2000) only observed cognitive effects in their heavy caffeine users, whereas in their low caffeine consumers (similar to the present sample), caffeine was only found to increase thirst. Furthermore, the 6 mg differential is smaller than any reported positive effect of caffeine on cognition, suggesting that the effects of High CGA Decaf reported here were more likely due to differences between the conditions other than caffeine content. Nevertheless, the possibility still remains that the level of caffeine present in the decaffeinated coffees was not inert, and thus the effects attributed to CGAs in the High CGA Decaf should also be considered with respect to this possible confounding effect. Variability in sleep quality was also not recorded and controlled for in the present study, and this could have had a potential mediating effect on the observed results. Finally, we note that on some measures there are marked baseline differences between the treatments. While baseline and the corresponding difference scores were used as a means of removing day-to-day variability, the issue surrounding the use of a baseline is controversial, and it is possible that differences in baseline scores may have influenced our treatment effects.

Future research in humans may benefit by addressing the following areas. By means of a CGA dose–response study, the optimal dose and time-related effects of the High CGA Decaf should be determined. Furthermore, the constituents and main derivatives of High CGA Decaf should be isolated and compared to determine whether the acute behavioral effects of this coffee is due to CGA or synergistic effects between coffee polyphenols (Yoshida et al. 2008). Finally, the chronic effects of High CGA Decaf and/or its main constituents should be assessed to determine whether there are long-term benefits. Given that caffeine is typically assumed to underlie the positive effects of coffee, having a clearer understanding of the particular compounds or combination of compounds underlying coffee effects will aid psychopharmacology more generally.

In summary, the current pilot study indicates that acute administration of decaffeinated coffee with high total CGA exerts some positive mood and mood-related behavioral effects. Despite the exploratory nature of the study, and a potential confounding effect of caffeine present in our decaffeinated coffees, our results suggest that chlorogenic acid compounds are active and may confer neuro-cognitive benefits, thus warranting further investigation.

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