Special Article

NUTRITION REVIEWS

Acute effects of tea constituents L-theanine, caffeine, and epigallocatechin gallate on cognitive function and mood: a systematic review and meta-analysis

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A systematic review and meta-analysis was conducted on 11 randomized placebo-controlled human studies of acute effects of tea constituents L-theanine and epigallocatechin gallate, administered alone or in combination with caffeine, on cognitive function and mood. The outcome measures of mood were alertness, calmness, and contentedness, derived from the Bond-Lader scales, and state anxiety, from the State-Trait Anxiety Inventory. Cognitive measures assessed were attentional switch, intersensory attention, and rapid visual information processing. Standardized mean differences between placebo and treatment groups are presented for each study and outcome measure. Meta-analysis using a random-effects model was conducted when data were available for three or more studies. Evidence of moderate effect sizes in favor of combined caffeine and L-theanine in the first 2 hours postdose were found for outcome measures Bond-Lader alertness, attentional switching accuracy, and, to a lesser extent, some unisensory and multisensory attentional outcomes. Moderator analysis of caffeine and L-theanine doses revealed trends toward greater change in effect size for caffeine dose than for L-theanine dose, particularly during the first hour post dose.

INTRODUCTION

Tea, a beverage prepared from the leaves of *Camellia sinensis*, has been consumed extensively throughout human history. Epidemiological studies have linked the consumption of tea (including green, black, and oolong varieties) to a number of beneficial outcomes for brain health, including a decreased incidence of cognitive decline[1–4] and lower levels of depression and psychological distress.[5,6] It was not until recent years, however, that randomized controlled trials (RCTs) have been conducted to investigate the acute effects of isolated tea constituents on cognition and mood. The major constituents of green tea include the tea catechins, which typically account for 30–42% of the dry weight of brewed green tea, along with the amino acid γ-*N*-ethylglutamine (L-theanine) and caffeine, which contribute around 3% and 2–5%, respectively, to both green and black varieties.[7] The four major tea catechins are (-)-epigallocatechin gallate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin gallate (ECG), and (-)-epicatechin (EC). Of these, EGCG is the most prominent, accounting for 50–80% of total catechins.[8]

Caffeine is known to increase acetylcholine and dopamine transmission in the brain, due to the inhibition of adenosine (A1 and A2a) receptors, with both of these neurotransmitters implicated in attention, arousal, and higher cognitive functions. Due to caffeine's rapid absorption following oral consumption, with peak plasma levels being reached within 30 minutes, acute effects on cognitive function and mood would be expected within this time period.[9] In comparison with

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caffeine, relatively less is known about the tea constituent L-theanine, although available preclinical data suggest it has effects in the central nervous system, including glutamate reuptake inhibition and the potentiation of γ-aminobutyric acid (GABA), DA, and serotonin.[10] Due to potentiation of the brain's main inhibitory transmitter GABA, it could be argued that L-theanine might act as a mild anxiolytic, which is consistent with its traditional use as a relaxation-promoting agent.[11] In contrast to caffeine, L-theanine is not absorbed as quickly, with peak plasma levels being reached around 50 minutes after oral consumption.[12] For this reason, it might be expected that the acute effects of L-theanine may lag behind the effects of caffeine. With regard to the tea catechins, little is known about their acute mechanisms of action in the brain, although one study suggests EGCG may acutely improve endothelial function and nitric oxide supply, with relevance for cognitive function.[13,14] Time to peak plasma levels of EGCG following oral consumption has been reported to be around 80 minutes, while absorption times for EGC and EC are considerably longer.[15]

While a number of studies have been conducted to investigate the acute nootropic effects of caffeine used in isolation,[9] relatively few human RCTs have been conducted to investigate the acute effects of L-theanine and EGCG, either by themselves or in combination with caffeine, on cognitive function and mood. Data demonstrating acute neurocognitive benefits associated with both L-theanine[16–19] and EGCG[14,20] have recently begun to emerge, yet a systematic examination to quantify these effects using standardized cognitive and mood assessments is yet to be conducted. Thus, the aim of the current review was to conduct a meta-analysis of existing RCTs in order to assess the evidence for acute effects of L-theanine and EGCG on cognitive function and mood.

METHODS

Article searching

An open-ended, language-restricted (English) search of MEDLINE (PubMed), Scopus, and the Cochrane Library was conducted for all available literature up until January 31, 2013, using seven terms pertaining to various tea constituents: ("Tea" OR "Theanine" OR "*Theanine" OR "Green Tea" OR "Black Tea" OR "Catechin*" OR "EGCG") in combination with seven terms pertaining to cognitive and mood assessments: ("Cogniti*" OR "Memory" OR "Attention*" OR "Neurocogniti*" OR "Executive Function" OR "Processing Speed" OR "Mood" OR "Stress" OR "Anxiety" OR "Well-being"). All searches were limited to human studies, clinical trials, or meta-analysis. Forward and backward searching was also performed on trials meeting the inclusion criteria using Scopus.

Trial selection

The following inclusion criteria were required: 1) must include a healthy (nonclinical) adult sample; 2) must be an RCT; 3) must involve oral administration of green tea, black tea, or one (or more) of the following tea constituents: L-theanine, ECGC, ECG, EGC, EC; 4) must measure cognitive and/or mood outcomes associated with acute administration of tea constituent(s). As an additional criterion, studies involving caffeine administration were included in the review, but only if caffeine was administered in combination with other tea constituents (e.g., L-theanine). A list of all studies and outcome measures included in the review is displayed in Table 1.[10,14,21–29]

Outcome measures of mood

The following outcome measures of mood were included in the systematic review/meta-analysis. Only measures that were used across four or more individual studies were included: Bond-Lader visual analog scales, the Caffeine Research visual analog scale ("alert" subscale), and the State-Trait Anxiety Inventory (STAI).

Bond-Lader visual analog scales. Bond-Lader visual analog mood scales[30] comprise a total of 16 adjective antonym pairs at each end of a 100-mm horizontal line, e.g., happy-sad, sociable-withdrawn, and calm-excited. Participants mark their current subjective state between the antonyms on the line, and each line is scored as the percentage of the total distance from the negative anchor. Three affective dimensions are calculated on the basis of scores from the 16 adjective pairs, representing the factors "alert," "content," and "calm."

Caffeine Research visual analog scales. The Caffeine Research visual analog scales (Caff-VAS) consist of seven visual analog scales ("relaxed," "alert," "jittery," "tired," "tense," "headache," and "overall mood"), each followed by a 100-mm horizontal line. The left end of each line is labeled "not at all," and the right end of each line is labeled "extremely." Participants mark their current subjective state as a point between the two extremes, with their answer scored from 0 to 100.[31] For the purposes of the current review, only the Caff-VAS "alert" scale was used, and it was considered sufficiently similar to the Bond-Lader "alert" to be included in meta-analysis.

State-Trait Anxiety Inventory. The STAI[32] comprises two scales. The "State" (STAI-S) subscale is a widely used

Table 1 **Summary of studies and outcome measures included in the meta-analysis.**

Reference	Treatment	Sample size	Age (y)	Mood outcomes	Cognitive outcomes	Caffeine withdrawal
Wightman et al. (2012)[21]	EGCG:135 /270 mg	27 (11M, 16F)	18–30	Caff-VAS alert	RVIP	>15 h
Scholey et al. (2012)[14]	EGCG: 300 mg	31 (12M, 19F)	mean = 27.74	B-L alert, calm, content	RVIP	>10 h
Higashiyama et al. (2011)[22]	L-Theanine: 200 mg	18	18–20	STAI-S	–	>24 h
De Bruin et al. (2011)[23]	L-Theanine: S1: 46; S2 :36 mg[a] Caffeine: S1: 100; S2: 90 mg[a]	S1: 26 (6M, 20F) S2: 32 (7M, 15F)	mean = 30.7 mean = 30.3	B-L alert, calm, content	Attentional switch, intersensory attention	>15 h
Giesbrecht et al. (2010)[25]	L-Theanine: 97 mg Caffeine: 40 mg	44 (16M, 28F)	18–34	B-L alert, calm, content	Attentional switch	>12 h
Einöther et al. (2010)[24]	L-Theanine: 97 mg Caffeine: 40 mg	29 (11M, 18F)	18–45	B-L alert, calm, content	Attentional switch, intersensory attention	>12 h
Owen et al. (2008)[26]	L-Theanine: 100 mg Caffeine: 50 mg	27 (14M, 13F)	mean = 28.3	B-L alert, calm, content	Attentional switch, RVIP	>12 h
Haskell et al. (2008)[27]	L-Theanine: 250 mg Caffeine: 150 mg	24 (9M, 15F)	18–34	B-L alert, calm, content	RVIP	>12 h
Rogers et al. (2008)[28]	L-Theanine: 200 mg Caffeine: 250 mg	48	Young	STAI-S, Caff-VAS alert	–	Not restricted
Kimura et al. (2007)[29]	L-Theanine: 200 mg	12 (12M)	20–25	STAI-S[b]	–	>9 h
Lu et al. (2004)[10]	L-Theanine: 200 mg	16 (12M, 4F)	18–34	B-L alert, calm, content, STAI-S	–	>24 h

Abbreviations: BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory-II; B-L, Bond-Lader; Caff-VAS, Caffeine Research visual analog scales; EGCG, (-)-epigallocatechin gallate; F, females; M, males; RVIP, Rapid visual information processing; STAI-S, Speilberger State-Trait Anxiety Inventory; VAS, visual analog scales.

[a] Administered as separate drinks over the course of the study.

[b] Used combined theanine-2 data from both low- and high-anxiety propensity groups. Also included an acute stressor of mental arithmetic.

instrument for measuring fluctuating levels of anxiety. The subscale contains 20 statements (e.g., "I am calm"). Participants are required to rate how much they feel like each statement at the time of making the response by marking a 4-point scale ranging from "not at all" to "very much so." Scores on both sections of the STAI range from 20 to 80, with higher scores indicating greater levels of anxiety.

Outcome measures of cognitive function

The outcome measures of cognitive function shown below were included in the systematic review/meta-analysis. As with the mood outcomes, only cognitive measures that were used across four or more individual studies were included: the attention switching task, the intersensory attention task, and the Rapid Visual Information Processing (RVIP) task.

Attention switching task. The attention switching task measures the ability to shift attention between different task sets.[33] Participants are presented with both a letter and a number on either side of a central fixation point. Left and right positioning of the letters and numbers vary randomly across trials. At every fourth presentation, the color of the letters and numbers changes between red and purple. When the stimuli appear in red, the participant is required to attend to the letter and respond with a button press only if the letter is a vowel. When the stimuli appear in purple, the participant is required to attend to the number and respond with a button press only if the number is even.[26]

Intersensory attention task. The intersensory attention task measures the ability to selectively attend to stimuli presented in the visual and auditory modalities. At the beginning of each trial, participants are cued as to which modality (visual or auditory) they will need to attend. Two visual stimuli are then presented that can differ in orientation, and/or two auditory stimuli are presented that can differ in pitch, with participants required to perform a discrimination task in the cued modality. Stimuli are presented either in isolation (unisensory) or in combination (intersensory).[24]

Rapid Visual Information Processing task. The RVIP task is a test of sustained attention that loads heavily on working memory. Single digits (1–9) are presented continuously in the middle of a computer screen in a semi-random order. Participants are required to press the response button as soon as they detect three consecutive odd or three even digits in ascending order (i.e., 2,4,6; 3,5,7; 4,6,8; 5,7,9). The digits are presented at a rate of 100 digits per minute, and there are typically 8 targets per minute. The outcome measures analyzed in the current review were the total proportion of correct responses (accuracy) and the reaction time for correct responses.

Data handling and statistical analysis

Since the majority of studies included in the review derive from crossover (paired) designs, estimates of variance (standard deviations [SDs]) in change scores were necessary to properly account for within-person differences. For this reason, mean change from baseline scores, together with the SD of baseline changes, were calculated for each outcome measure included in the review. Once the correlation between baseline and post-treatment outcomes was accounted for, then subsequent correlations between changes from baseline for different treatment periods were assumed to be zero (independent).[34] In cases where the data necessary for these calculations were not available in the published manuscript, the original authors were contacted in order to obtain either the raw data required for these calculations or the summary data for each treatment group, which consisted of mean change from baseline scores, along with SDs of these changes. Changes from baseline and SDs were used in all cases, with the exception of data for studies from the Unilever group,[23–26] where estimates for post-treatment means and SDs were provided after first co-varying for baseline scores.

All statistical meta-analysis and graphical display were conducted using the "metafor" package (version 1.7-0) in "R" version 3.0.0.[35] First, for each cognitive and mood outcome measure and time point, standardized mean differences (SMDs) between placebo and treatment group means were calculated by dividing the mean difference by the pooled SD of the two groups. The SMD was corrected for positive bias using the method outlined by Hedges and Olkin.[36] In cases where data for comparable outcome measures and treatments within a 60-minute time window were available for ≥3 studies, a meta-analysis was conducted. Meta-analysis was conducted using a random-effects model, with average effect size presented as average SMD, for both the first hour (outcome measurement occurring within the interval 10–50 min postdose) and the second hour (outcome measurement occurring within the interval 50–120 min postdose) separately. In cases where more than one measurement was conducted in the second hour, the measurement commencing closest to 60 minutes postdose was used (refer to Tables 2–6 for specific study selections). Restricted maximum-likelihood estimation was used to estimate τ^2, and the Knapp & Hortung adjustment was applied to the standard errors of the estimated coefficients. The Knapp & Hortung adjustment helps to account for uncertainty in the estimate of τ^2

Table 2 **Standardized mean differences (SMDs), calculated using Hedges' g between treatment and placebo, for Bond-Lader visual analog mood scales. Bold print indicates an SMD >±0.3.**

Reference	Dose (mg)			Time (min)	Bond-Lader VAS SMD (SD)		
	Caffeine	L-Theanine	EGCG		Alert	Calm	Content
Scholey et al. (2012)[14]	–	–	300	120	0.01 (0.25)	**0.54** (0.26)	0.14 (0.25)
Wightman et al. (2012)[21]	–	–	135	45–90	–0.12 (0.27)	–	–
	–	–	270	45–90	–0.01 (0.27)	–	–
De Bruin et al. (2011)[23]	50	23	–	10–50[a]	**0.68** (0.29)	–0.15 (0.28)	0.10 (0.28)
study 1	100	46	–	60–100[b]	**0.83** (0.30)	**–0.59** (0.29)	0.25 (0.29)
De Bruin et al. (2011)[23]	30	12	–	10–40[a]	**0.44** (0.25)	0.03 (0.25)	0.27 (0.25)
study 2	60	24	–	50–80[b]	0.26 (0.25)	0.07 (0.25)	0.28 (0.25)
	90	36	–	90–120	**0.44** (0.25)	–0.02 (0.25)	0.18 (0.25)
Giesbrecht et al. (2010)[25]	40	97	–	20–50[a]	**0.43** (0.22)	–0.17 (0.21)	0.10 (0.21)
	40	97	–	70–100[b]	**0.40** (0.22)	–0.13 (0.21)	–0.04 (0.21)
Einöther et al. (2010)[24]	40	97	–	10–50[a]	**–0.51** (0.27)	**0.31** (0.26)	0.01 (0.26)
	40	97	–	60–100[b]	**–0.40** (0.27)	**0.42** (0.27)	–0.01 (0.27)
Owen et al. (2008)[26]	50	100	–	60–75[b]	0.08 (0.27)	–0.03 (0.27)	–0.17 (0.27)
	50	100	–	90–105	0.17 (0.27)	**0.33** (0.27)	0.00 (0.27)
	50	–	–	60–75	**0.37** (0.27)	–0.17 (0.27)	–0.10 (0.27)
	50	–	–	90–105	**0.38** (0.27)	0.26 (0.27)	–0.03 (0.27)
Haskell et al. (2008)[27]	150	250	–	30–60[a]	**0.76** (0.30)	**–0.38** (0.29)	**0.42** (0.29)
	150	250	–	90–120[b]	**0.49** (0.29)	**–0.30** (0.29)	**0.38** (0.29)
	–	250	–	30–60	–0.06 (0.29)	**0.37** (0.29)	**0.52** (0.29)
	–	250	–	90–120	–0.01 (0.29)	0.20 (0.29)	**0.45** (0.29)
	150	–	–	30–60	0.22 (0.29)	0.06 (0.29)	**0.32** (0.29)
	150	–	–	90–120	0.20 (0.29)	–0.01 (0.29)	0.18 (0.29)
Rogers et al. (2008)[28]	250	200	–	50–70[b]	**0.42** (0.41)	–	–
	–	200	–	50–70	**0.30** (0.41)	–	–
	250	–	–	50–70	**0.98** (0.43)	–	–

Abbreviations: EGCG, (-)-epigallocatechin gallate; SD, standard deviation; VAS, visual analog scale.
[a] Studies included in meta-analysis for the first hour.
[b] Studies included in meta-analysis for the second hour.

in the context of random- and mixed-effects models and generally leads to more conservative *P* values.[35] Cochran's *Q* test was used to test for significant heterogeneity in effect sizes ($\tau^2 \neq 0$). Studies with a standardized residual *z* value >±2.5 were treated as outliers and removed from the model. The presence of bias was investigated using Begg's adjusted rank correlation[37] and Egger's weighted least squares regression test,[38] where standard error of effect size was used as the predictor. Exploratory analysis of the effects of caffeine and L -theanine doses as moderator variables was also conducted using a mixed-effect model. Predicted values for effect sizes as a function of caffeine and L -theanine dose were calculated on the basis of the mixed model, using intercept and β coefficients values.

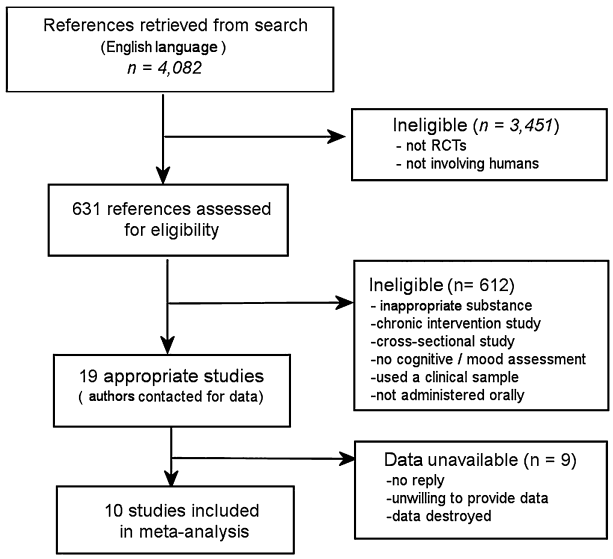

Figure 1 Meta-analysis flow chart.

RESULTS

Of the 4,082 studies located, 19 were considered to be relevant RCTs. As detailed in Figure 1, of the 19 relevant studies, 9 were excluded at the final stage, leaving 10 studies for review (11 studies when both substudies by De Bruin et al.[23] were included).

Outcome variables for mood

Bond-Lader mood ratings. Data for Bond-Lader visual analog scales were available from nine studies.[14,21,23–28] SMDs for each study are presented in Table 2 according to each subscale (alert, calm, and content), treatment, and time point.

Sufficient data were available to conduct two meta-analyses on Bond-Lader subscales for treatments containing an L-theanine and caffeine combination: 1) during the first hour postdose; and 2) during the second hour postdose.

For Bond-Lader "alert" ratings, five studies were initially included in the meta-analysis for the first hour (10–50 min),[23–25,27] although the study by Einöther et al.[24] was found to be an outlier in the model (z value = –3.77) and was subsequently excluded from the final model. Using a random-effects model ($k = 4$, $Q(3) = 1.23$, $P > 0.05$, $I^2 = 0\%$), the average SMD was estimated to be 0.542 (SE = 0.08), in favor of tea constituents ($t = 6.57$, $P < 0.01$). No evidence of bias was found (Begg, $P = 0.087$; Egger, $P = 0.084$). Moderator analysis using a mixed-effects model ($k = 4$, $Q(1) = 0.15$, $P > 0.05$) revealed no significant effects for caffeine or L-theanine dose (caffeine: $\beta = 0.0059$/mg, $P > 0.05$; L-theanine: $\beta = –0.0019$/mg, $P > 0.05$). For Bond-Lader "alert" ratings in the second hour (50–120 min), seven studies were included in the initial meta-analysis,[23–28] although the study by Einöther et al.[24] was also found to be an outlier (z value = –2.81) and was subsequently excluded. Using a random-effects model ($k = 6$, $Q(5) = 3.90$, $P > 0.05$, $I^2 = 0\%$) the average SMD was estimated to be 0.392 (SE = 0.10), in favor of tea constituents ($t = 3.96$, $P < 0.05$). No evidence of bias was found (Begg, $P = 0.496$; Egger, $P = 0.652$). Moderator analysis using a mixed-effects model ($k = 6$, $Q(3) = 3.24$, $P > 0.05$) revealed no significant effects for caffeine or L-theanine dose (caffeine: $\beta = 0.0021$/mg, $P > 0.05$; L-theanine: $\beta = –0.0009$/mg, $P > 0.05$). Forest plots for the results of the Bond-Lader "alert" meta-analysis in the first and second hours postdose[23,25–28] are displayed in Figure 2.

For Bond-Lader "calm" ratings, five studies were included in the meta-analysis for the first hour (10–50 min).[23–25,27] Using a random-effects model ($k = 5$, $Q(4) = 3.66$, $P > 0.05$, $I^2 = 0\%$), the average SMD was estimated to be –0.069 (SE = 0.11), which was nonsignificant. No evidence of bias was found (Begg, $P = 0.817$; Egger, $P = 0.921$). Moderator analysis using a mixed-effects model ($k = 5$, $Q(2) = 2.03$, $P > 0.05$) revealed no significant effects for caffeine or L-theanine dose (caffeine: $\beta = –0.0054$/mg, $P > 0.05$; L-theanine: $\beta = 0.0011$/mg, $P > 0.05$). For Bond-Lader "calm" in the second hour (50–120 min), six studies were included in the meta-analysis.[23–27] Using a random-effects model ($k = 6$, $Q(5) = 7.69$, $P > 0.05$, $I^2 = 32.7\%$), the average SMD was estimated to be –0.081 (SE = 0.13), which was nonsignificant. No evidence of bias was found (Begg, $P = 0.469$; Egger, $P = 0.655$). Moderator analysis using a mixed-effects model ($k = 6$, $Q(3) = 4.10$, $P > 0.05$) revealed no significant effects for caffeine or L-theanine dose (caffeine: $\beta = –0.0070$/mg, $P > 0.05$; L-theanine: $\beta = 0.0018$/mg, $P > 0.05$).

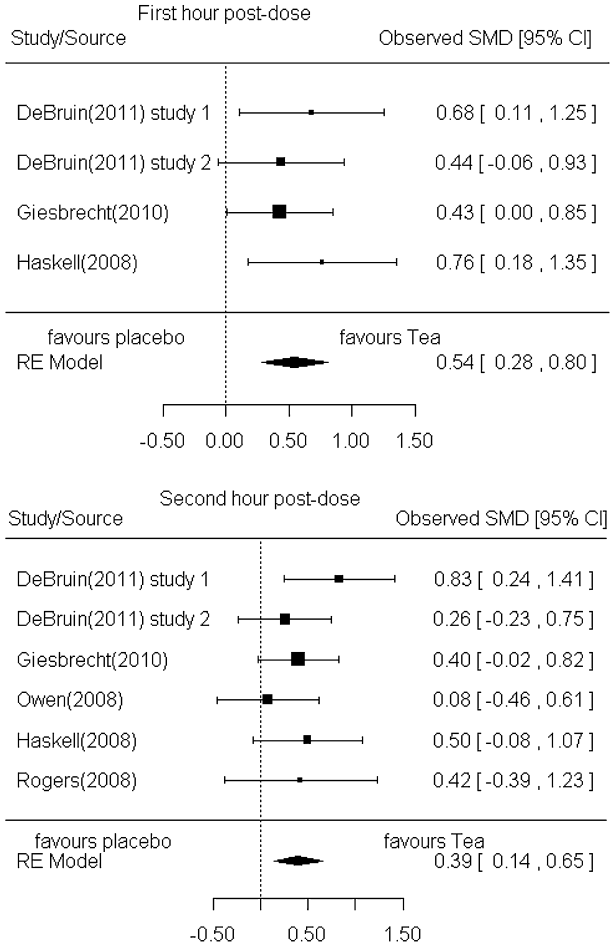

Figure 2 Forest plot for Bond-Lader "alert" ratings (first and second hours postdose) for caffeine and L-theanine combination versus placebo.

For Bond-Lader "content" ratings, five studies were included in the meta-analysis for the first hour (10–50 min).[23–25,27] Using a random-effects model ($k = 5$, $Q(4) = 1.4466$, $P > 0.05$, $I^2 = 0\%$), the average SMD was estimated to be 0.169 (SE = 0.11), which was nonsignificant. No evidence of bias was found (Begg, $P = 0.83$; Egger, $P = 0.510$). Moderator analysis using a mixed-effects model ($k = 5$, $Q(2) = 0.54$, $P > 0.05$) revealed no significant effects for caffeine or L-theanine dose (caffeine: $\beta = 0.0046$/mg, $P > 0.05$; L-theanine: $\beta = –0.0013$/mg, $P > 0.05$). For Bond-Lader "content" ratings in the second hour (50–120 min), six studies were included in

Table 3 **Standardized mean differences (SMDs), calculated using Hedges' g, between treatment and placebo, for State-Trait Anxiety Inventory (STAI-S). Bold print indicates an SMD >0.3.**

Reference	Dose (mg)			Time (min)	STAI-S SMD (SD)
	Caffeine	L-Theanine	EGCG		
Rogers et al. (2008)[28]	250	200	–	50–70	−0.06 (0.41)
	250	–	–	50–70	0.08 (0.41)
	–	200	–	50–70[a]	**−0.42** (0.41)
Higashiyama et al. (2011)[22]	–	200	–	15	0.21 (0.33)
	–	200	–	30	**0.33** (0.34)
	–	200	–	45[a]	0.10 (0.33)
	–	200	–	60	0.25 (0.33)
Kimura et al. (2007)[29]	–	200	–	20	**−0.84** (0.43)
	–	200	–	30	0.07 (0.41)
	–	200	–	40[a]	0.13 (0.41)
Lu et al. (2004)[10]	–	200	–	150–300	0.17 (0.35)

Abbreviations: EGCG, (-)-epigallocatechin gallate; SD, standard deviation.
[a] Studies included in meta-analysis.

the meta-analysis.[23–27] Using a random-effects model ($k = 6$, $Q(5) = 3.30$, $P > 0.05$, $I^2 = 0\%$), the average SMD was estimated to be 0.100 (SE = 0.09), which was nonsignificant. No evidence of bias was found (Begg, $P = 0.469$; Egger, $P = 0.377$). Moderator analysis using a mixed-effects model ($k = 6$, $Q(3) = 0.81$, $P > 0.05$) revealed no significant effects for caffeine or L-theanine dose (caffeine: $\beta = 0.0055$/mg, $P > 0.05$; L-theanine: $\beta = -0.0014$/mg, $P > 0.05$).

State-Trait Anxiety Inventory. Data for STAI-S were available from four studies.[10,22,28,29] SMDs are presented in Table 3 according to each treatment and time point. For the study by Lu et al.,[10] SDs for the change from baseline (baseline to postdose) data were not available. For this study, the SD was estimated assuming a $\rho = 0.5$ correlation between pre- and postdose scores, according to the following formula[34]: $SD^{Difference} = sqrt[(SD^{Postdose})^2 + (SD^{Baseline})^2 - (2 \times \rho \times SD^{Postdose} \times SD^{Baseline})]$. For STAI-S ratings, sufficient data were available to conduct one meta-analysis for treatments containing 200 mg of L-theanine at 40–70 minutes postdose. Three studies were included in the meta-analysis.[22,28,29] Using a random-effects model ($k = 3$, $Q(2) = 1.20$, $P > 0.05$, $I^2 = 0\%$), the average SMD was estimated to be −0.04 (SE = 0.17), which was nonsignificant. No evidence of bias was found (Begg, $P = 0.333$; Egger, $P = 0.640$). Moderator analysis was not possible due to insufficient variance in L-theanine doses.

Outcome variables for cognitive function

Attention switching. Data for attention switching (both reaction times and accuracy) were available from five studies.[23–26] SMDs for each study are presented in Table 4 according to each treatment and time point.

Sufficient data were available to conduct meta-analyses on the effects of combined caffeine and L-theanine on attention switching in both the first and second hours. For the first hour (10–50 min), four studies were included in analyzing reaction time and accuracy data.[23–25] Using a random-effects model ($k = 4$, $Q(3) = 0.82$, $P > 0.05$, $I^2 = 0\%$), the average SMD for reaction time was estimated to be −0.191 (SE = 0.07), which was nonsignificant. No evidence of bias was found (Begg, $P = 0.750$; Egger, $P = 0.867$). Moderator analysis using a mixed-effects model ($k = 4$, $Q(1) = 0.04$, $P > 0.05$) revealed no significant effects for caffeine or L-theanine dose (caffeine: $\beta = 0.0165$/mg, $P > 0.05$; L-theanine: $\beta = 0.0002$/mg, $P > 0.05$). For accuracy in the first hour (10–50 min), using a random-effects model ($k = 4$, $Q(3) = 0.42$, $P > 0.05$, $I^2 = 0\%$), the average SMD was estimated to be 0.384 (SE = 0.05), in favor of tea ($t = 8.18$, $P < 0.01$). No evidence of bias was found (Begg, $P = 0.750$; Egger, $P = 0.873$). Moderator analysis using a mixed-effects model ($k = 4$, $Q(2) = 0.03$, $P > 0.05$) revealed no significant effects for caffeine or L-theanine dose (caffeine: $\beta = 0.0116$/mg, $P > 0.05$; L-theanine: $\beta = 0.0002$/mg, $P > 0.05$).

For the second hour postdose (50–120 min), five studies were included in analyzing reaction time and accuracy data.[23–26] Using a random-effects model ($k = 5$, $Q(4) = 3.61$, $P > 0.05$, $I^2 = 0\%$), the average SMD for reaction time was estimated to be −0.159 (SE = 0.11), which was nonsignificant. No evidence of bias was found (Begg, $P = 1.00$; Egger, $P = 0.908$). Moderator analysis using a mixed-effects model ($k = 5$, $Q(2) = 2.24$, $P > 0.05$) revealed no significant effects for caffeine or L-theanine dose (caffeine: $\beta = 0.0078$/mg, $P > 0.05$; L-theanine: $\beta = 0.0017$/mg, $P > 0.05$). For accuracy in the second hour (50–120 min), using a random-effects model ($k = 5$, $Q(4) = 2.31$, $P > 0.05$, $I^2 = 0\%$), the average SMD was

Table 4 **Standardized mean differences (SMDs) between treatment and placebo for attention switching. Bold print indicates an SMD >±0.3.**

Reference	Dose (mg)			Time (min)	SMD (SD)	
	Caffeine	L-Theanine	EGCG		Reaction time	Accuracy
De Bruin et al. (2011)[23]	50	23	–	10–50[a]	–0.03 (0.28)	**0.50** (0.29)
study 1	100	46	–	60–100[b]	0.22 (0.28)	**0.44** (0.29)
De Bruin et al. (2011)[23]	30	12	–	10–40[a]	–**0.36** (0.25)	0.26 (0.25)
study 2	60	24	–	50–80[b]	0.27 (0.25)	**0.30** (0.25)
	90	36	–	90–120	0.00 (0.25)	**0.46** (0.25)
Giesbrecht et al. (2010)[25]	40	97	–	20–50[a]	–0.15 (0.21)	**0.42** (0.22)
	40	97	–	70–100[b]	–0.07 (0.21)	**0.36** (0.21)
Einöther et al. (2010)[24]	40	97	–	10–50[a]	–0.21 (0.26)	**0.37** (0.26)
	40	97	–	60–100[b]	–0.19 (0.07)	**0.40** (0.27)
Owen et al. (2008)[26]	50	100	–	60–75[b]	–**0.49** (0.28)	–0.07 (0.27)
	50	100	–	90–105	–0.15 (0.27)	0.00 (0.27)
	50	–	–	60–75	–0.28 (0.27)	0.03 (0.27)
	50	–	–	90–105	0.02 (0.27)	0.09 (0.27)

Abbreviations: EGCG, (-)-epigallocatechin gallate; SD, standard deviation.
[a] Studies included in meta-analysis for the first hour.
[b] Studies included in meta-analysis for the second hour.

estimated to be 0.2937 (SE = 0.09), in favor of tea ($t = 3.40$, $P < 0.05$). No evidence of bias was found (Begg, $P = 0.817$; Egger, $P = 0.747$). Moderator analysis using a mixed-effects model ($k = 5$, $Q(2) = 2.13$, $P > 0.05$) revealed no significant effects for caffeine or L-theanine dose (caffeine: $\beta = 0.0006$/mg, $P > 0.05$; L -theanine: $\beta = -0.0013$/mg, $P > 0.05$). Forest plots for the results of the attention switching accuracy meta-analyses in the first and second hours postdose[23–26] are displayed in Figure 3.

Intersensory attention. Data for attention switching (both reaction times and accuracy) were available from three studies.[23,24] SMDs for each study are presented in Table 5 according to each treatment and time point.

Sufficient data were available to conduct a meta-analysis on the effects of combined caffeine and L-theanine on unisensory auditory attention in both the first and second hours. There were insufficient degrees of freedom to conduct moderator analysis. For the first hour (10–50 min postdose), three studies were included in the analysis of reaction time and accuracy data.[23,24] Using a random-effects model ($k = 3$, $Q(2) = 0.28$, $P > 0.05$, $I^2 = 0\%$), the average SMD for reaction time was estimated to be –0.1524 (SE = 0.06), which was nonsignificant. No evidence of bias was found (Begg, $P = 1.00$; Egger, $P = 0.635$). For accuracy, in a random-effects model ($k = 3$, $Q(2) = 0.20$, $P > 0.05$, $I^2 = 0\%$), the SMD was estimated to be –0.1264 (SE = 0.05), which was also nonsignificant. No evidence of bias was found (Begg, $P = 0.333$; Egger, $P = 0.113$). For the second hour (50–120 min postdose), the same three studies were included in the meta-analysis of unisensory auditory attention data. Using a random-effects model ($k = 3, Q(2) = 2.65, P > 0.05, I^2 = 18.64\%$), the average SMD for reaction time was estimated to be –0.175

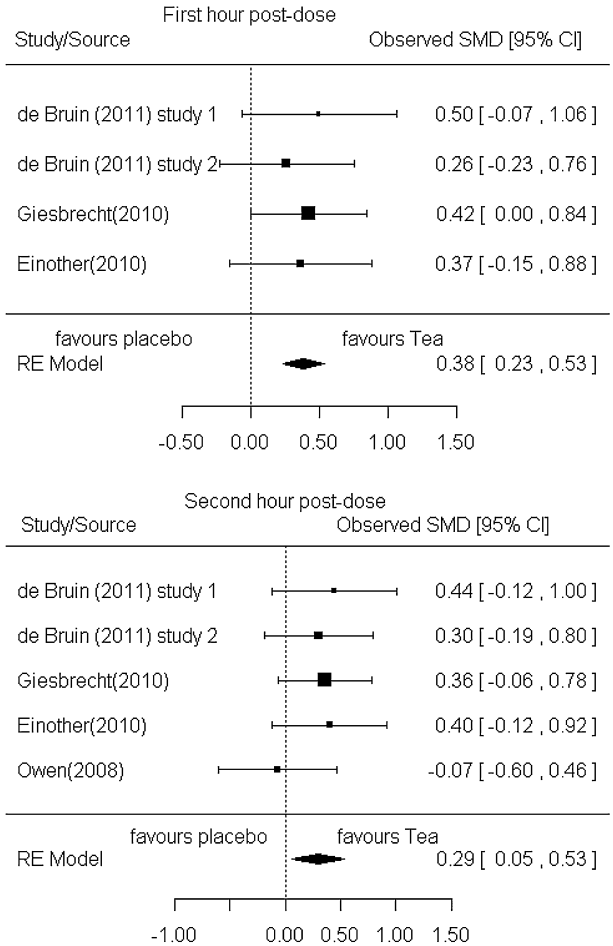

Figure 3 Forest plot for attention switching accuracy (first and second hours postdose) for caffeine and L-theanine combination versus placebo.

Table 5 **Standardized mean differences (SMDs) between treatment and placebo for unisensory and multisensory attention. Bold print indicates an SMD >±0.3.**

Study	Dose (mg)		Time (min)	Auditory attention SMD (SD)		Visual attention SMD (SD)	
	Caffeine	L-Theanine		Reaction time	Accuracy	Reaction time	Accuracy
Unisensory							
De Bruin et al. (2011)[23] study 1	50	23	10–50[a]	–0.18 (0.31)	–0.20 (0.28)	**0.35** (0.34)	0.10 (0.28)
	100	46	60–100[b]	0.23 (0.31)	0.29 (0.28)	–0.27 (0.34)	0.19 (0.28)
De Bruin et al. (2011)[23] study 2	30	12	10–40[a]	–0.05 (0.25)	–0.04 (0.25)	0.18 (0.26)	0.19 (0.25)
	60	24	50–80[b]	–0.24 (0.25)	**0.30** (0.25)	0.03 (0.26)	**0.44** (0.25)
	90	36	90–120	0.05 (0.25)	**0.30** (0.25)	–0.04 (0.26)	**0.57** (0.25)
Einöther et al. (2010)[24]	40	97	10–50[a]	–0.25 (0.27)	–0.16 (0.28)	–0.11 (0.28)	0.14 (0.26)
	40	97	60–100[b]	**–0.43** (0.28)	0.15 (0.26)	0.12 (0.28)	0.02 (0.29)
Multisensory							
De Bruin et al. (2011)[23] study 1	50	23	10–50[a]	–	–	–0.16 (0.31)	**0.75** (0.29)
	100	46	60–100[b]	–	–	**–0.69** (0.32)	**0.57** (0.29)
De Bruin et al. (2011)[23] study 2	30	12	10–40[a]	0.17 (0.37)	–0.02 (0.25)	0.29 (0.26)	0.22 (0.25)
	60	24	50–80[b]	**0.66** (0.38)	**0.34** (0.25)	–0.05 (0.26)	0.17 (0.25)
	90	36	90–120	–0.22 (0.37)	–0.26 (0.25)	0.00 (0.26)	0.29 (0.25)
Einöther et al. (2010)[24]	40	97	10–50[a]	0.26 (0.27)	–0.08 (0.26)	0.03 (0.27)	0.16 (0.26)
	40	97	60–100[b]	–0.02 (0.27)	–0.14 (0.25)	**–0.45** (0.28)	**0.19** (0.26)

Abbreviations: SD, standard deviation.
[a] Studies included in meta-analysis for the first hour.
[b] Studies included in meta-analysis for the second hour.

(SE = 0.19), which was nonsignificant. No evidence of bias was found (Begg, $P = 1.00$; Egger, $P = 0.460$). For accuracy, in a random-effects model ($k = 3$, $Q(2) = 0.20$, $P > 0.05$, $I^2 = 0\%$), the SMD was estimated to be 0.247 (SE = 0.05), in favor of tea ($t = 5.10$, $P < 0.05$). No evidence of bias was found (Begg, $P = 1.00$; Egger, $P = 0.965$).

For unisensory visual attention, sufficient data were also available to conduct a meta-analysis on the effects of combined caffeine and L-theanine in both the first and second hours. There were insufficient degrees of freedom to conduct moderator analysis. For the first hour (10–50 min), three studies were included in the analysis of reaction time and accuracy data.[23,24] Using a random-effects model ($k = 3$, $Q(2) = 1.16$, $P > 0.05$, $I^2 = 0\%$), the average SMD for reaction time was estimated to be 0.117 (SE = 0.13), which was nonsignificant. No evidence of bias was found (Begg, $P = 1.00$; Egger, $P = 0.615$). For accuracy, in a random-effects model ($k = 3$, $Q(2) = 0.05$, $P > 0.05$, $I^2 = 0\%$), the SMD was estimated to be 0.147 (SE = 0.03), in favor of tea ($t = 5.8126$, $P < 0.05$). No evidence of bias was found (Begg, $P = 0.333$; Egger, $P = 0.128$). For the second hour (50–120 min), the same three studies were included in the meta-analysis of unisensory auditory attention data. Using a random-effects model ($k = 3$, $Q(2) = 0.83$, $P > 0.05$, $I^2 = 0\%$), the average SMD for reaction time was estimated to be −0.01 (SE = 0.11), which was nonsignificant. No evidence of bias was found (Begg, $P = 1.00$; Egger, $P = 0.299$). For accuracy, in a random-effects model ($k = 3$, $Q(2) = 1.34$, $P > 0.05$, $I^2 = 0\%$), the SMD was estimated to be 0.22 (SE = 0.13), which was nonsignificant. No evidence of bias was found (Begg, $P = 1.00$; Egger, $P = 0.707$).

There were not sufficient data available to conduct a meta-analysis on multisensory auditory attention ($k = 2$), although sufficient data were available to conduct a meta-analysis on multisensory visual attention data in both the first and second hours (k = 3[23,24]). There were insufficient degrees of freedom to conduct moderator analysis with only three studies. Using a random-effects model ($k = 3$, $Q(2) = 1.34$, $P > 0.05$, $I^2 = 0\%$), the average SMD for reaction time in the first hour (10–50 min) was estimated to be 0.078 (SE = 0.13), which was nonsignificant. No evidence of bias was found (Begg, $P = 0.333$; Egger, $P = 0.245$). For accuracy in the first hour (10–50 min), in a random-effects model ($k = 3$, $Q(2) = 2.65$, $P > 0.05$, $I^2 = 19.94\%$), the SMD was estimated to be 0.35 (SE = 0.18), which was nonsignificant. No evidence of bias was found (Begg, $P = 1.00$; Egger, $P = 0.265$). For the second hour (50–120 min), the same three studies were included in the meta-analysis of unisensory visual attention data. Using a random-effects model ($k = 3$, $Q(2) = 2.65$, $P > 0.05$, $I^2 = 25.05\%$), the average SMD for reaction time was estimated to be −0.364 (SE = 0.19), which was nonsignificant. No evidence of bias was found

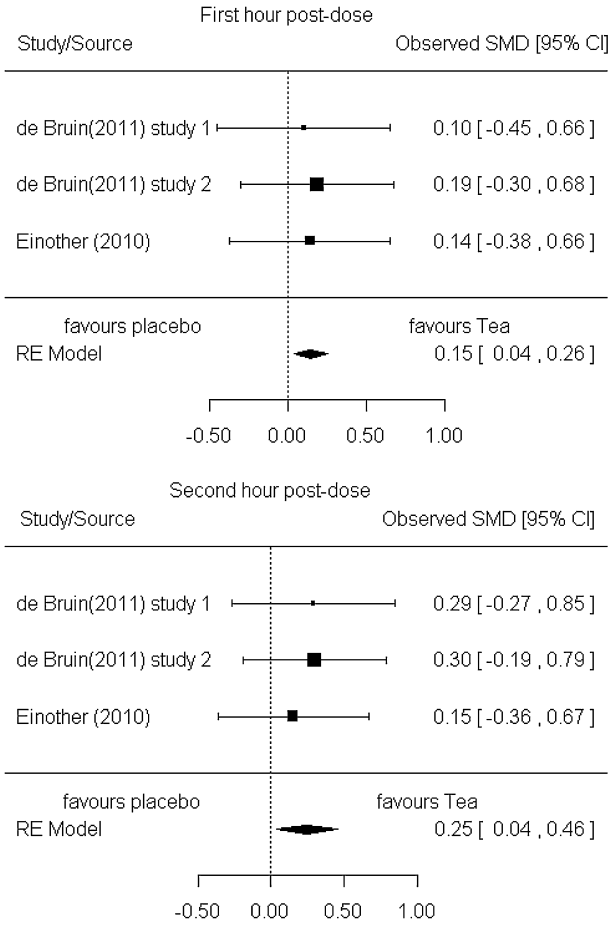

Figure 4 Forest plot for unisensory visual attention accuracy in the 1st hour and unisensory auditory attention accuracy in the 2nd hour for caffeine and L-theanine combination versus placebo.

(Begg, $P = 0.333$; Egger, $P = 0.254$). For accuracy, in a random-effects model ($k = 3$, $Q(2) = 1.32$, $P > 0.05$, $I^2 = 0\%$), the SMD was estimated to be 0.288 (SE = 0.12), which was nonsignificant. No evidence of bias was found (Begg, $P = 0.333$; Egger, $P = 0.190$). Forest plots for the significant results of the meta-analysis of intersensory attention accuracy in the first and second hours postdose[23,24] are displayed in Figure 4.

Rapid visual information processing. Data for RVIP (both reaction times and accuracy) were available from four studies.[14,21,26,27] SMDs for each study are presented in Table 6 according to each treatment and time point. Insufficient data were available to conduct a meta-analysis.

DISCUSSION

Mood effects

Tea containing a combination of both caffeine and L-theanine was found to induce acute increases in Bond-Lader alertness ratings that were of moderate effect size in the first hour (SMD = 0.542). In comparison of the individual studies included in the analysis, it is apparent that caffeine dose may be associated to some extent with the differences in effect sizes across the four studies. With 50 mg of caffeine, a slightly larger effect size was observed in the first (SMD = 0.68) versus the second study (SMD = 0.44) by De Bruin et al.,[23] in which only 30 mg of caffeine was administered. In the study by Giesbrecht et al.,[25] which used a dose of caffeine (40 mg) similar to that used by De Bruin et al.[23] in their second study, the effect size was also comparable (SMD = 0.43). Similarly, in the study by Haskell et al.,[27] in which 150 mg of caffeine

Table 6 **Standard mean differences (SMD) between treatment and placebo for rapid visual information processing. Bold print indicates an SMD >±0.3.**

Reference	Dose (mg)			Time (min)	SMD (SD)	
	Caffeine	L-Theanine	EGCG		Reaction time	Accuracy
Scholey et al. (2012)[14]	–	–	300	120	–0.29 (0.26)	–0.04 (0.26)
Wightman et al. (2012)[21]	–	–	135	45–90	0.08 (0.28)	0.27 (0.28)
	–	–	270	45–90	–0.12 (0.28)	0.07 (0.28)
Haskell et al. (2008)[27]	150	250	–	30–60	–**0.52** (0.29)	**0.93** (0.3)
	150	250	–	90–120	–**0.35** (0.29)	**0.89** (0.3)
	–	250	–	30–60	0.18 (0.29)	0.16 (0.29)
	–	250	–	90–120	–0.16 (0.29)	0.16 (0.29)
	150	–	–	30–60	–**0.33** (0.29)	**0.47** (0.29)
	150	–	–	90–120	–0.21 (0.29)	**1.14** (0.31)
Owen et al. (2008)[26]	50	100	–	60–75	–0.04 (0.27)	–0.14 (0.27)
	50	100	–	90–105	–0.13 (0.27)	0.10 (0.27)
	50	–	–	60–75	–0.10 (0.27)	–0.02 (0.27)
	50	–	–	90–105	–**0.33** (0.27)	0.04 (0.27)

Abbreviations: EGCG, (-)-epigallocatechin gallate; SD, standard deviation.

was administered, the largest effect size for Bond-Lader alertness in the first hour was observed (SMD = 0.76). In contrast, L-theanine dose does not appear to be associated with the observed changes in alertness, as evidenced by a dose (97 mg) that is four times larger in the Giesbrecht et al.[25] study than in the second study by De Bruin,[23] while the effect sizes for alertness are very similar (SMD = 0.43 versus 0.44, respectively). While moderator analysis did not indicate that caffeine could explain a significant proportion of effect size variance, this lack of a positive association may be attributable to the limited number of studies included in the analysis. With regard to the study by Einöther et al.,[24] which was found to be an outlier in the first hour, it is not immediately apparent why a moderate reduction in alertness (SMD = −0.40 to −0.51) was reported, since the treatments and sample characteristics for the studies by Giesbrecht et al.[25] and Einöther et al.[24] were very similar.

The finding of a smaller effect size for Bond-Lader "alertness" in the second hour postdose (SMD = 0.392), following combined caffeine and L-theanine administration, can similarly be interpreted as evidence of reductions in blood plasma levels of caffeine, in line with pharmacokinetic data that suggests peak plasma levels are obtained at around 30 minutes postdose.[9] With the exception of study 1 by De Bruin et al.,[23] in which a larger effect size was found during the second hour postdose (SMD = 0.83), alertness was found to be either comparable (e.g., Giesbrecht et al.,[25] SMD = 0.40) or decreased (De Bruin et al.[23] study 2, SMD = 0.26; and Haskell et al.,[27] SMD = 0.50) in the second versus the first hour postdose across all studies. A likely reason for the increase in alertness observed in study 1 by De Bruin et al.[23] was that, due to the staggered treatment administration used in this study, an additional 50 mg of caffeine had just been consumed by participants around 10 minutes before repeat testing. It is noteworthy that in the study by Owen et al.,[26] which was included for the first time in the second hour postdose analysis, caffeine and L-theanine in combination were not found to affect alertness any more than placebo. While this study administered only a relatively low dose of caffeine (50 mg) in combination with 100 mg of L-theanine, it is not immediately apparent why the effect size was smaller than that in the study by Giesbrecht et al.,[25] in which similar doses of caffeine (40 mg) and L-theanine (97 mg) were used. It is also interesting to note that in the study by Rogers et al.,[28] a comparable effect size (SMD = 0.42) for alertness was found in the second hour compared with the other studies, even though caffeine abstinence was not enforced as a study day restriction.

Although there were insufficient studies to conduct meta-analysis on the effects of L-theanine in isolation, it is noteworthy that in the study by Haskell et al.,[27] in which 250 mg of L-theanine was administered in isolation, no treatment effect on alertness was reported (SMD = −0.06 in the first hour, and SMD = −0.01 in the second hour). However, in the study by Rogers et al.,[28] a small effect size was reported in the second hour in response to 200 mg of L-theanine administered alone (SMD = 0.30). Further data containing varying doses of L-theanine administered in isolation would be necessary to more accurately determine the differential effect of L-theanine on alertness. However, predicted values for effect sizes as a function of L-theanine and caffeine in combination suggest a trend whereby predicted effect sizes for alertness are much greater following caffeine administration than L-theanine administration (see Figure 5). In relation to EGCG, while only two studies were included in this review, preliminary data suggest that doses in the range of 135–300 mg of EGCG do not affect alertness ratings acutely during the second hour postdose (SMD range = −0.12 to 0.01).

For Bond-Lader calmness ratings, meta-analysis did not reveal a significant effect for administration of caffeine and L-theanine in combination. The direction of the effect was inconsistent across studies. Moderate reductions in calmness were reported in both the first study by De Bruin et al.[23] and the study by Haskell et al.,[27] with SMDs of −0.15 and −0.38 during the first hour and SMDs of −0.59 and −0.30 during the second hour, respectively. In contrast, an increase in calmness was noted in the study by Einöther et al.,[24] with an SMD of 0.31 in the first hour and 0.42 in the second hour, and in the study by Owen et al.[26] during the second hour (SMD = 0.33). Again, moderator analysis did not indicate that caffeine or L-theanine dose significantly contributed to effect sizes, and there were little data available to examine the individual contributions of caffeine or L-theanine administered in isolation. However, in the study by Haskell et al.,[27] 150 mg of caffeine in isolation had no noticeable effect on calmness ratings. Similarly, in the study by Owen et al.,[26] 50 mg of caffeine in isolation also had negligible effects. However, it is intriguing that when 250 mg of L-theanine was administered in isolation (Haskell et al.[27]), a small increase in calmness was observed during both the first and second hours (SMD = 0.37 and 0.20, respectively). Indeed, predicted values for calmness rating effect sizes as a function of caffeine and L-theanine dose in combination suggest trends whereby predicted effect sizes for calmness ratings decrease as caffeine dose increases, and increase gradually as L-theanine dose increases (see Figure 5). In relation to EGCG, while data were available from only one study (Scholey et al.[14]), it is noteworthy that these preliminary data suggest that 300 mg of EGCG results in moderately increased calmness during the second hour postdose (SMD = 0.54).

For Bond-Lader content ratings, meta-analysis also did not reveal a significant effect for the administration of caffeine and L-theanine in combination. Across four of

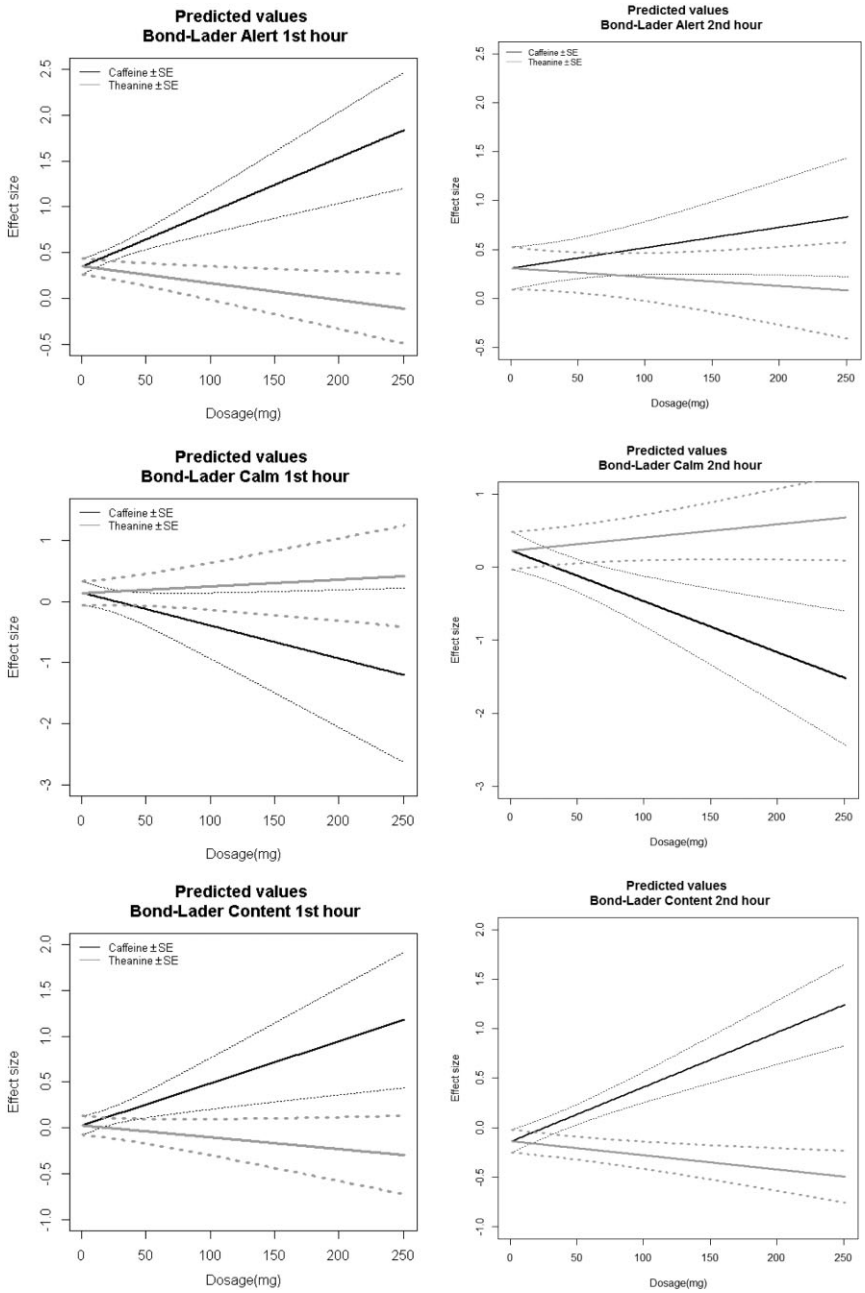

Figure 5 Predicted values for Bond-Lader scales as a function of caffeine and theanine dose during the first and second hours postdose. Predicted values for caffeine dose with $_{L}$-theanine dose = 0. Predicted values for $_{L}$-theanine dose with caffeine dose = 0.

the studies included in the analysis,[23–26] effect sizes were very small, only ranging from −0.17 to 0.28. However, it is of interest that in the study by Haskell et al.,[27] in which high doses of both caffeine (150 mg) and L-theanine (250 mg) were administered in combination, a small-moderate increase in contentment was reported for both the first and second hours (SMD = 0.42 and 0.38, respectively). Again, moderator analysis did not indicate the caffeine or L-theanine dose could explain a significant proportion of the variance in effect sizes. However, predicted values for effect sizes as a function of caffeine and L-theanine doses in combination suggest a trend whereby contentment increases as a function of caffeine dose (particularly in the first hour), while contentment decreases as a function of L-theanine dose in the first hour and remains relatively unchanged as a function of dose in the second hour (see Figure 5).

In contrast, in the study by Owen et al.,[26] in which 100 mg of caffeine was administered in isolation, no noticeable effect on contentment was reported (SMD =

–010 for the first hour, and SMD = –0.03 for the second hour). Similarly, in the study by Haskell et al.,[27] only a small effect on contentment rating was reported following 150 mg of caffeine (SMD = 0.32 in the first hour, and SMD = 0.18 in the second hour). Contrary to the predicted effect sizes derived from a combination of L-theanine and caffeine, when 250 mg of L-theanine was administered in isolation (Haskell et al.[27]), a moderate effect on contentment was observed (SMD = 0.52 in the first hour, and SMD = 0.45 in the second hour). In light of this finding, it is suggested that further data using a wider range of L-theanine doses will be required to more accurately determine the individual contribution of L-theanine to ratings of contentment. In relation to EGCG, while data were available from only one study (Scholey et al.[14]), it is interesting that these preliminary data suggest that 300 mg of EGCG resulted in only a negligible effect on contentment ratings in the second hour postdose (SMD = 0.14).

For state anxiety ratings (STAI-S), meta-analysis on the effects of 200 mg of L-theanine at 40–50 minutes postdose did not reveal any significant effects on anxiety. In the study by Kimura et al.,[29] a strong reduction in state anxiety (SMD = –0.84) was reported after 20 minutes in comparison with placebo. However, it is important to note that this measurement was made at the end of a mental arithmetic task that was designed to elicit a stress response. This time point was also too early to be included in the meta-analysis for STAI-S and L-theanine. In the subsequent measurements made at 30 minutes and 40 minutes, while the participants were at rest, no further reductions in STAI-S were noted (Kimura et al.[29]). These findings provide preliminary evidence to suggest that L-theanine may ameliorate the effects of acute stress, yet may not noticeably reduce baseline levels of anxiety. In the study by Rogers et al.,[28] however, a reduction in STAI-S (SMD = –0.42) was also noted 50 minutes after administration of 200 mg of L-theanine, without an acute stressor. Interestingly, no such reductions in STAI-S were noted at 50 minutes for 250 mg of caffeine or for 250 mg of caffeine in combination with 200 mg of L-theanine in the same study (Rogers et al.[28]). In contrast, in the study by Higashiyama et al.,[22] small increases in STAI-S ratings were noted from 15 to 60 minutes following administration of 200 mg of L-theanine versus placebo (maximum SMD = 0.33 at 30 min). However, it is important to note that this sample included a certain proportion of high-anxiety-prone individuals. While it would not be expected that these participants would respond differentially to placebo and L-theanine, conclusions derived from such a sample should be viewed with caution. Finally, in the study by Lu et al.,[10] no noticeable effect on STAI-S was observed with 200 mg of L-theanine from 150–300 minutes postdose under relaxed conditions. In order to better understand the effect of theanine on anxiety, further studies utilizing a larger range of L-theanine doses are required.

Cognitive effects

In relation to attention switching, the combination of caffeine and L-theanine appeared to have a stronger effect on accuracy than on reaction times. In the meta-analysis of reaction times, a small-moderate effect size was observed (SMD = 0.384) in the first hour, while a slightly smaller effect size was observed in the second hour (SMD = 0.294). Across four of the studies,[23–25] increases in attention switch accuracy in the first and second hours were consistently small-medium (SMDs of 0.26–0.50). However, in the study by Owen et al.,[26] no noticeable effects on accuracy were observed with either 50 mg of caffeine in isolation or 50 mg of caffeine in combination with 100 mg of L -theanine. These findings parallel the results obtained by Owen et al.[26] for Bond-Lader alertness, since effectively no attentional gains were found for combined caffeine and L-theanine versus placebo. Again, moderator analysis did not indicate that caffeine or L-theanine dose could explain a significant proportion of the variance in effect sizes. However, predicted values for effect sizes as a function of caffeine and L-theanine doses in combination highlight a trend whereby attention switch accuracy increases rapidly as a function of caffeine in the first hour and remains relatively unchanged in the second hour as a function of increasing caffeine dose. For L-theanine, the predicted values for effect sizes suggest that L-theanine dose has little effect on attention switching accuracy in the first hour and only marginal effects on accuracy in the second hour, with a trend toward a gradual decrease in accuracy as L-theanine dose increases (see Figure 6).

In relation to reaction times in the attention switching task, very small improvements in reaction time were observed across most studies in the first 2 hours postdose. Interestingly, the largest effect size improvements in reaction time were observed in study 2 by De Bruin et al.[23] from 10–40 minutes (SMD = –0.36) and in the study by Owen et al.[26] from 60–75 minutes (SMD = –0.49), when improvements in accuracy were low (SMD = 0.26 and –0.07, respectively). Speed-accuracy trade-off is one explanation of these findings, although it is not immediately apparent whether dose of caffeine or of L-theanine is responsible for the effects. Moderator analysis did not indicate that caffeine or L-theanine dose could explain a significant proportion of the variance in effect sizes. However, predicted values for effect sizes as a function of caffeine and L-theanine doses in combination suggest trends whereby attention switch reaction time increases rapidly as a function of caffeine dose in the first hour and increases more gradually as a function of caffeine dose in

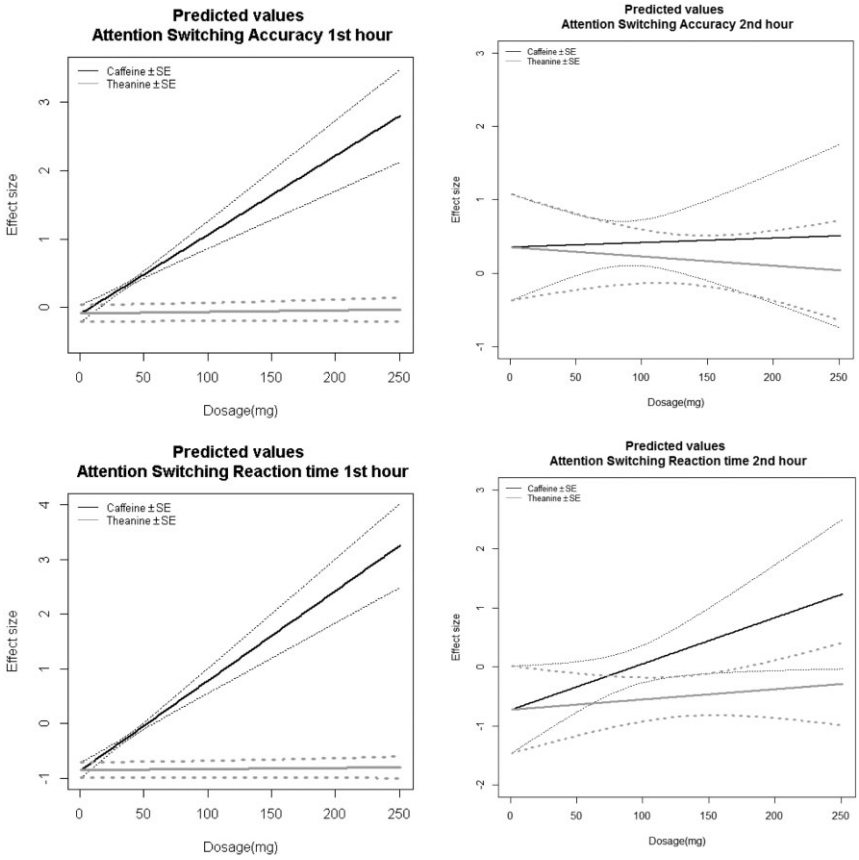

Figure 6 Predicted values for attention switching task accuracy and reaction time as a function of caffeine and $_{L}$-theanine dose during the first and second hours. (Predicted values for caffeine dose with $_{L}$-theanine dose = 0. Predicted values for $_{L}$-theanine dose with caffeine dose = 0).

the second hour. For L-theanine, reaction times appear to be moderately impaired (SMD = −0.7) in the first hour, regardless of dose, and remain impaired in the second hour but improve marginally as function of dose (see Figure 6). Again, studies that utilize L-theanine in isolation are required to better differentiate performance gains associated with L-theanine from those associated with caffeine when analyzing both accuracy and reaction time data using the attentional switch paradigm.

For meta-analysis of the effects of combined caffeine and L-theanine on unisensory auditory attention, only accuracy in the second hour postdose was found to be significantly affected, with a small effect size observed (SMD = 0.247). However, in the study by Einöther et al.,[24] a small-moderate improvement in reaction time was observed in the second hour using a relatively high dose of L-theanine (97 mg) in combination with 40 mg of caffeine (SMD = −0.43). For meta-analysis of the effects of combined caffeine and L-theanine on unisensory visual attention, only accuracy in the first hour postdose was found to be significantly affected, with a small effect size observed (SMD = 0.147). It is noteworthy that in the second study by De Bruin et al.,[23] an increase in accuracy of moderate effect size was observed from both 50–80 minutes and 50–120 minutes (SMDs = 0.44 and 0.57, respectively). A possible explanation for this discrepancy is that the tea treatments were administered three times over the course of 90 minutes (baseline, 40 min and 80 min), so it could be expected that the blood plasma levels of caffeine and L-theanine would have been higher than if the total dose was administered as a single dose. Considering the low levels of L-theanine in this study, it is most likely that this increase in accuracy was attributable to the total of 90 mg of caffeine administered over the course of the study.

In relation to the analysis of multisensory data for combined caffeine and L-theanine administration, insufficient data were available to conduct meta-analysis on the auditory data, and no clear trend could be observed across studies. However, it is interesting to note that in the second study by De Bruin et al.,[23] a small increase in accuracy (SMD = 0.34) was observed in conjunction with a moderate slowing of reaction time (SMD = 0.66). An explanation for this performance decrease is not immediately apparent. Meta-analysis of the multisensory visual attention data revealed no significant improvement in either

accuracy or reaction time for combined caffeine and L-theanine administration. However, it is interesting that in the first study by de Bruin et al.,[23] a moderate-large increase in accuracy was observed in both the first and second hours (SMDs = 0.75 and 0.57, respectively). Similarly, in the same study, a moderate improvement in reaction time was also observed during the second hour postdose (–0.69), a result most likely attributable to the 100 mg of caffeine. Moreover, in the study by Einöther et al.,[24] a moderate improvement in reaction time was observed in the second hour postdose (SMD = –0.45), although this followed a relatively higher dose of L-theanine (97 mg). Interestingly, in comparison with the attention switching task, used in many of the same studies/samples, the effect sizes were generally not as large for either unisensory or multisensory attention tasks, suggesting that perhaps these tasks are not as sensitive to the effects of caffeine and L-theanine. However, considering only three studies were included in the analysis, further data using wider dose ranges are warranted.

Finally, in relation to RVIP, the study by Haskell et al.[27] revealed improvements in accuracy of large effect size following 150 mg of caffeine and 250 mg of L-theanine in both the first and second hours (SMDs = 0.93 and 0.98, respectively), together with small-moderate improvements in reaction time (SMDs = –0.52 and –0.35, respectively). Similarly, following 150 mg of caffeine administered in isolation, improvements in RVIP accuracy of large effect size were also observed (SMD = 0.47 for the first hour, and SMD = 1.14 for the second hour). A small improvement in reaction time was also observed for the first hour (SMD = –0.33)[27]. In the study by Owen et al.,[26] an improvement in reaction time was also observed for the second hour postdose following 100 mg of caffeine in isolation (SMD =–0.33). Since no noticeable effects on RVIP accuracy or reaction time were observed when L-theanine was administered in isolation, these findings suggest that caffeine is most likely responsible for RVIP performance improvements. In contrast, for EGCG, no evidence of improvement in RVIP performance was observed by Scholey et al.[14] or Wightman et al.[21] when using doses of 135 mg, 270 mg, or 300 mg over the first 2 hours postadministration.

As a final comment, it is important to acknowledge that the psychopharmacological study of tea constituents is an emerging research area, and that much more empirical data are required before reliable predictions can be made about the acute effects of the varied constituents. The findings of the current systematic review were based on what is currently only a limited number of studies, and for this reason the conclusions should be revisited when further data become available. Future studies investigating the acute cognitive and mood effects associated with green tea catechins and L-theanine, administered in the absence of caffeine, will also be of great utility in further elucidating the dose-response relationships associated with these substances. The consistent use of outcome measures and postdose sampling times across different studies will help facilitate future synthesis of research findings. With regard to the latter, greater attention to the pharmacokinetics of specific substances may also help to better align peak plasma levels with acute effects. The analysis of the studies in the current review by first- and second-hour groupings was necessitated by the wide range of time points employed across the studies. Since caffeine dose not reach peak plasma levels until after 30 minutes,[9] and times to reach peak plasma levels are even slower for L-theanine (>50 min) [12]and tea catechins (>80 min),[15] it is possible that some of the acute effects associated with these substances may not have been captured during the time frame that was studied.

CONCLUSION

Tea constituents L-theanine and caffeine in combination were found to induce increases in Bond-Lader alertness of moderate effect size in the first hour, and increases in alertness of small-moderate effect size in the second hour postdose (SMD = 0.542 and 0.392, respectively). Similarly, L-theanine and caffeine in combination were also found to induce increases in attention switching accuracy during both the first and second hours postdose of small-moderate effect size (SMD = 0.384 and 0.294, respectively). Small enhancement of unisensory visual attention accuracy was also found following L-theanine and caffeine consumption in the first hour postdose (SMD = 0.147). Similarly, small enhancement of unisensory auditory attention accuracy was found following L-theanine and caffeine consumption in the second hour postdose (SMD = 0.247). Moderator analysis did not reveal significant effects of caffeine and L-theanine dose on effect size, although analysis of trends in predicted values suggests that the majority of the attention-enhancing effects can be attributed to caffeine dose. Insufficient data were available to conduct meta-analysis on EGCG's psychopharmacological effects, although preliminary evidence suggests that EGCG may have a calming effect during the second hour postdose. Future research using a greater range of doses for both L-theanine and EGCG in isolation is required to more accurately determine their effects on cognition and mood, and to dissociate these effects from those of caffeine.

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