

L-Theanine and Caffeine in Combination Affect Human Cognition as Evidenced by Oscillatory alpha-Band Activity and Attention Task Performance¹⁻³

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Abstract

Recent neuropharmacological research has suggested that certain constituents of tea may have modulatory effects on brain state. The bulk of this research has focused on either L-theanine or caffeine ingested alone (mostly the latter) and has been limited to behavioral testing, subjective rating, or neurophysiological assessments during resting. Here, we investigated the effects of both L-theanine and caffeine, ingested separately or together, on behavioral and electrophysiological indices of tonic (background) and phasic (event-related) visuospatial attentional deployment. Subjects underwent 4 d of testing, ingesting either placebo, 100 mg of L-theanine, 50 mg of caffeine, or these treatments combined. The task involved cued shifts of attention to the left or right visual hemifield in anticipation of an imperative stimulus requiring discrimination. In addition to behavioral measures, we examined overall, tonic attentional focus as well as phasic, cue-dependent anticipatory attentional biasing, as indexed by scalp-recorded alpha-band (8–14 Hz) activity. We found an increase in hit rate and target discriminability (d') for the combined treatment relative to placebo, and an increase in d' but not hit rate for caffeine alone, whereas no effects were detected for L-theanine alone. Electrophysiological results did not show increased differential biasing in phasic alpha across hemifields but showed lower overall tonic alpha power in the combined treatment, similar to previous findings at a larger dosage of L-theanine alone. This may signify a more generalized tonic deployment of attentional resources to the visual modality and may underlie the facilitated behavioral performance on the combined ingestion of these 2 major constituents of tea. *J. Nutr.* 138: 1572S–1577S, 2008.

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Introduction

In recent years, several potential health benefits of drinking tea (*Camellia sinensis*) have come to light through systematic study of the effects of its constituent compounds (1,2). Although anecdotal evidence abounds, the psychological and neurophysiological effects of tea have received relatively little experimental investigation and thus remain unclear. Popular claims have centered on generalized state changes such as the reduction of stress and induction of relaxed wakefulness. Psychopharmacological studies have indeed demonstrated mood effects that support these claims and have further shown that tea affects elements of cognition (3,4). Although caffeine (1,3,7-trimethylxanthine) is by far the constituent most studied, with findings of increased alertness and speeded reaction time (RT)⁴ predominant (5,6), there exists evidence that caffeine alone cannot fully account for the positive effects of tea drinking. Tea has been shown to raise skin

⁴ Abbreviations used: C, caffeine-alone condition; d' , discriminability index; EEG, electroencephalographic; EOG, electro-oculographic; P, placebo condition; RT, reaction time; T, theanine-alone condition; T+C, combined condition; TSE, temporal spectral evolution.

temperature to a higher level (7), to increase critical flicker fusion threshold (4), and to reduce physiological stress responses and increase relaxation ratings (8) when compared with coffee or other control beverages matched for caffeine level.

L-Theanine (γ -glutamylethylamide), a unique amino acid present almost exclusively in the tea plant, has recently received research interest in the neuroscience community with findings of neuroprotective effects [see Kakuda (9)] and mood effects indexed both by subjective self-reports (10) and via psychological and physiological responses to stress (11). Using electroencephalographic (EEG) recordings in humans, Kobayashi et al. (12) and Juneja et al. (13) reported that activity within the alpha frequency band (8–14 Hz) increased in reaction to L-theanine ingestion when measured during a state of rest. This was of interest to the attention community, as the alpha rhythm has long been known to be sensitive to overall attentional states (i.e., intensity aspects such as arousal) (14) and, further, is involved in the biasing of selective attention (15,16). In intersensory attention tasks, where the relevant modality is cued ~ 1 s before a compound audiovisual target stimulus, parieto-occipital alpha power in the intervening period is increased for attend-visual trials relative to attend-auditory trials (15,17). In Gomez-Ramirez et al. (18), this differential effect of cue information on anticipatory alpha amplitude was found to be larger on ingestion of 250 mg of L-theanine relative to placebo. In addition, tonic (background) alpha amplitude was relatively decreased for L-theanine, in apparent contradiction to the findings of Juneja et al. (13). In a follow-up study, we tested whether an analogous alpha-mediated attention effect seen in visuospatial attention tasks (16,19–22) is also affected by L-theanine ingestion (M. Gomez-Ramirez, S. P. Kelly, J. L. Montesi, and J. J. Foxe, unpublished results). L-Theanine, at a dosage of 250 mg, was not found to increase the differential effect of attention. However, in a replication of the previous intersensory attention study (18), overall tonic alpha was greatly reduced on L-theanine.

An immediate question, given this replication, is whether this tonic alpha reduction occurs at lower dosages of L-theanine, closer to the amount ingested through a typical serving of tea. In the present study, we administered a lower dosage of 100 mg to address this. Also of critical interest is whether the ingestion of caffeine, another major component of tea, exerts behavioral and/or neurophysiological effects during such a demanding visuospatial attention task, when ingested alone or when ingested together with L-theanine. Here we present data from a 4-d experiment using a balanced repeated-measures design, with subjects receiving either placebo (P), L-theanine alone (T), caffeine alone (C), or the combination of L-theanine plus caffeine (T+C) on each day. We assessed effects of treatment with regard to basic behavioral measures of RT and accuracy [including the so-called discriminability index (d'), which is independent of individual detection criteria], and in relation to both tonic and phasic attentional processes as indexed by alpha power.

Methods

Participants. Sixteen (5 female) neurologically normal paid volunteers, aged between 21 and 40 y (mean 27.5 y), participated in the study. All subjects provided written informed consent, and the Institutional Review Board of the Nathan S. Kline Institute for Psychiatric Research approved the experimental procedures. All subjects reported normal or corrected-to-normal vision. Four subjects were left-handed. The mean habitual tea consumption across the subjects was 3.7 cups/wk, and for coffee, 3.8 cups/wk (~ 250 mL/cup). Subjects arrived at the laboratory in the morning between 0900 and 1200 h, having abstained from all caffeinated beverages for the previous 24 h.

Treatment. The timing of treatment administration relative to testing was based on published reports of amino acid concentration and plasma concentration changes over time. L-Theanine concentration has been found to increase significantly within 1 h after administration in rats, to continue to increase gradually up to 5 h, and to decrease thereafter, with complete disappearance evident after 24 h (23). Peak plasma caffeine concentration is reached between 15 and 120 min postingestion in humans, with a variable half-life typically between 2.5 and 4.5 h (5). Accordingly, participants abstained from consuming caffeine for at least 24 h before testing and began experimental task runs 30 min after ingestion of any given treatment. Subjects underwent 4 d of testing, ingesting either placebo, 100 mg of L-theanine, 50 mg of caffeine, or these treatments combined. Subjects were uninformed of the treatment, which was served in 100 mL of water, with the placebo treatment consisting only of water. Both theanine and caffeine are tasteless in water solution.

Stimuli and task. Subjects were seated 150 cm from a CRT monitor and were instructed to maintain fixation on a central cross (white on midgray background) at all times. Each trial began with a centrally presented arrow cue (“S1”) of 100-ms duration, with equal probability pointing leftward or rightward toward 1 of 2 bilateral locations centered at a horizontal distance of 4.2° from the fixation cross and 1.2° above the horizontal meridian. Each location was marked by 4 dots outlining a $2.4^\circ \times 2.4^\circ$ square. The cue consisted of a circle of 1° diameter with an embedded arrow, designed to minimize any sensory effects related to physical differences between the left and right cues. The colors of the arrow and circle were red on green for half of the blocks of recording and green on red for the other half, with the order counterbalanced across subjects and days of testing. Red and green values were precalibrated for each subject to be approximately isoluminant by flicker photometry. Then, 933 ms after cue onset, a second imperative stimulus (“S2”) was presented at the left or right marked location (valid or invalid with respect to cue direction) with equal probability. The S2s (100 ms duration) consisted of either a white \times or + ($0.75^\circ \times 0.75^\circ$) embedded in a circular array of 8 small circles such that the overall stimulus diameter was 1.95° . The target stimulus was chosen randomly at the beginning of each experimental run of ~ 4.5 min, and thereafter standard and target stimuli were equally likely on each trial. Subjects were instructed to shift their attention covertly to the location indicated by the cue, to respond by pressing a mouse button with the index finger of the right hand when a target S2 appeared on that side, and to ignore stimuli appearing on the invalid side entirely. Trials were separated by a 1633-ms interval. A total of 100 trials were presented per run. Subjects completed 20 runs on each day of testing.

Data acquisition. Continuous EEG data, digitized at 512 Hz, were acquired from 164 scalp electrodes and 4 electro-oculographic (EOG) electrodes with a pass-band of 0.05–100 Hz. Off-line, the data were low-pass filtered up to 45 Hz and rereferenced to the nasion. Noisy channels, identified by taking the SD of amplitude over the entire run (from first to last stimulus presented) and checking whether it is $>50\%$ greater than that of at least 3 of the 6 closest surrounding channels, were interpolated. Horizontal EOG data were recorded using 2 electrodes placed at the outer canthi of the eyes, allowing measurement of eye movements during testing. Based on a calibrated mapping of EOG amplitude to visual angle, trials were rejected off-line if eye gaze deviated by $>0.5^\circ$ during the cue-target interval.

Behavioral data analysis. We employed a d' as our principal performance metric, taking into account the accuracy of responding on nontargets as well as targets and controlling for individual differences in detection criteria. The value of d' was derived from the hit rate (proportion of all valid targets detected) and false alarm rate (proportion of all valid nontargets incorrectly responded to), calculated only from trials containing no eye movements or artifacts. Ceiling effects on hit rate were corrected in the standard way by assuming 0.5 misses, and similarly, a floor effect of zero false alarms was corrected to 0.5. RT was measured as the time (in milliseconds) from the point of S2 onset at which the mouse button was correctly pressed in response to valid target trials.

To control for the potential confound of practice effects on the behavioral data, the order of treatments across the 4 d of testing was fully counterbalanced across subjects. This is a standard procedure and ensures unbiased comparison across conditions. However, in the case of the present data, the variance in behavioral measures arising from the day of testing (order effect) far superseded that arising from treatment. Thus, a normalization of these measures was necessary to remove the variance caused by practice, and this was carried out by transforming each data point to a z -score with respect to the mean and SD of all scores measured on that day (d 1, d 2, d 3, d 4). Because the distribution of scores for each day contains an equal number of data points from each treatment, it cannot result in any bias for treatment but, rather, optimizes statistical power to test for treatment effects.

Electrophysiological data analysis. EEG data were epoched from -300 ms before to 1100 ms after cue onset and baseline-corrected relative to the interval -100 to 0 ms, with an artifact rejection threshold of ± 100 μ V applied. Mean alpha amplitude was calculated using the temporal spectral evolution (TSE) technique (15). TSE is carried out simply by filtering each epoch with a passband of 8 – 14 Hz, rectifying, then averaging across trials. The averaged TSE waveforms were then smoothed by averaging data points within a sliding 100 -ms window.

The first analysis concerned tonic (background) alpha amplitude, which was found to decrease on L-theanine in our previous 2 studies (18, M. Gomez-Ramirez, S. P. Kelly, J. L. Montesi, and J. J. Foxe, unpublished results). Tonic alpha was measured as the integrated TSE amplitude within the baseline period -200 to 0 before the cue stimulus, regardless of the direction of attentional deployment (i.e., to the left or right hemifield). The dependent measure was computed as the baseline alpha amplitude averaged across 6 electrodes, chosen on the basis of the grand-average scalp distribution of alpha amplitude, collapsed across the 4 d.

In a second analysis, we tested lateralized, anticipatory alpha amplitude for effects of attention and possible interactions with treatment. We normalized alpha amplitude relative to baseline by dividing the TSE amplitude by the mean amplitude within the baseline interval (-200 to 0) and log-transforming, making the measure equivalent to a percentage change from baseline. This narrows down the analysis to attention-related differential activity, independent of tonic effects. The anticipatory alpha dependent measure was computed as the integrated TSE amplitude over the postcue interval 500 to 900 ms, ending just before the S2. Amplitude was averaged across 6 electrodes over each hemisphere, determined based on grand-average difference topographies (cue-left minus cue-right) collapsed across the 4 d.

Statistical methods. A 4-d balanced repeated-measures design was employed, with subjects receiving 1 of the 4 treatments (including placebo) on each day in counterbalanced order. SPSS for Windows (version 12.0) was used for all statistical analyses. Tests were conducted with an α level of 0.05 unless otherwise stated. In the analysis of behavioral data, we tested specifically for improvements in performance as a result of any of the 3 treatments. Thus, 1-tailed, paired t -tests ($df = 15$) were conducted between the placebo condition and each of the 3 treatments for hit rate, RT, and d' measures. Because 3 t -tests were performed including the same placebo data, we applied a Bonferroni-corrected α -level of 0.016 here.

To test for effects of tonic alpha amplitude, a 1-way ANOVA was carried out with the factor of treatment having the levels P, T, C, and T+C. Follow-up protected t tests were then conducted to unpack significant differences existing between each of the T, C, and T+C conditions and the P condition. Further post hoc paired comparisons among the 4 treatment conditions were conducted as appropriate through additional t -tests.

To test for effects on pretarget alpha amplitude a $4 \times 2 \times 2$ ANOVA was carried out with factors of treatment (P, T, C, T+C), attention (cue-left, cue-right), and hemisphere (left, right). To unpack a potential 3-way interaction, we reduced the alpha cueing effect (typically seen as a hemisphere \times attention interaction) to a single measure by adding the differential over the 2 hemispheres, i.e., subtracting cue-right from cue-left on the left hemisphere, subtracting cue-left from cue-right on the right hemisphere, and summing these 2 values. Thus reduced, testing of

treatment effects on the alpha cueing effect, as found in the analogous intersensory study of Gomez-Ramirez et al. (18), could be done via paired t -tests comparing each of the 3 treatments T, C, and T+C against P.

Results

Behavioral performance. Behavioral performance was significantly improved on the combined treatment (T+C) in terms of hit rate ($P < 0.016$) and d' ($P < 0.002$). There was also a significant improvement in d' on C compared with P ($P < 0.016$), but not in hit rate. There were no significant effects of L-theanine, and no effects of any of the 3 treatments on RT (Fig. 1).

Electrophysiology. There was a significant effect of treatment on tonic alpha amplitude ($P < 0.02$). Follow-up t -tests revealed that alpha was significantly lower for T+C than P ($P < 0.02$).

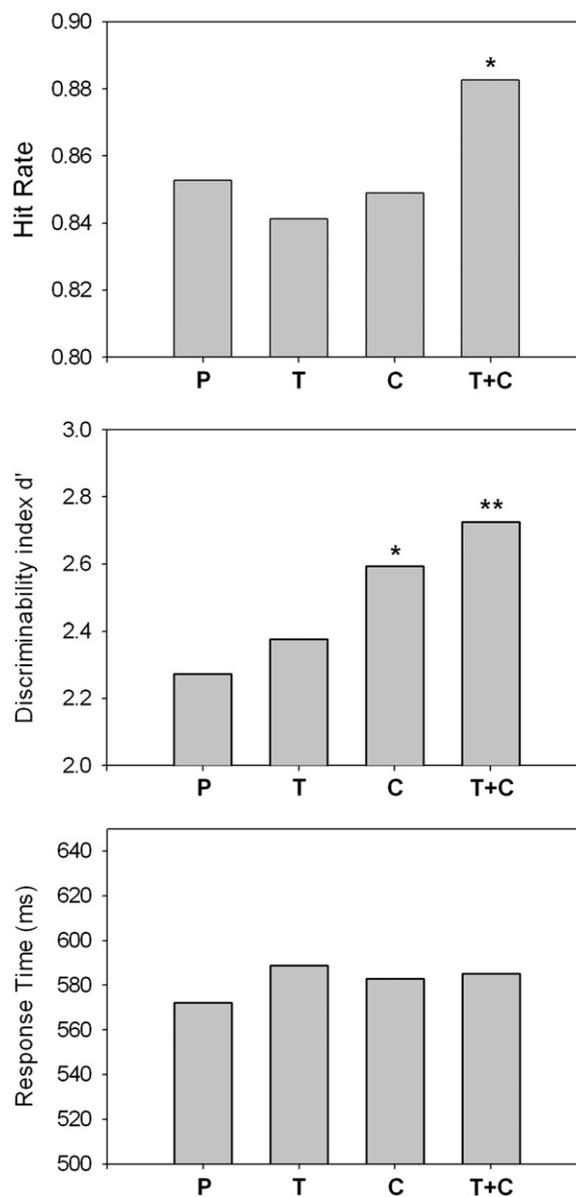


FIGURE 1 Mean hit rate (proportion of targets detected) (upper panel), mean d' (middle panel), and mean RT (lower panel) when subjects ingested placebo (P), L-theanine (T), caffeine (C), or these treatments combined (T+C). Values are means ($n = 16$). Asterisks indicate difference from P: * $P < 0.05$, ** $P < 0.01$).

P did not differ from either T or C (see Fig. 2). Tonic alpha differed between T+C and T ($P < 0.005$) but not between T+C and C.

The typical alpha cueing effect was readily apparent in both the nonnormalized alpha amplitude waveforms and normalized pretarget measures (Fig. 3) for each treatment day. A strong attention \times hemisphere interaction ($P < 0.0005$) was found on the pretarget anticipatory alpha measures as expected, reflecting the typically observed alpha-mediated cueing effect. In addition, there was a significant 3-way interaction among treatment, attention, and hemisphere ($P < 0.05$). When we reduced the alpha cueing effect to a single metric as described above, the effect was smaller on C than P ($P < 0.02$) but did not differ for the T or T+C conditions.

Discussion

This study was aimed at extending our knowledge of the effects of compounds contained in tea on the cognitive function of attention. Testing relatively low-dosage treatments of L-theanine alone (100 mg), caffeine alone (50 mg), and their combination, we observed an interesting pattern of effects for both behavioral and electrophysiological measures. Whereas no behavioral effects on hit rate were apparent for either treatment alone at the low dosages tested here, when both L-theanine and caffeine were ingested together, hit rate underwent an enhancement of $\sim 3\%$. In terms of d' , improvements were seen for both caffeine alone and L-theanine plus caffeine, the latter having a larger effect size (0.55 vs. 0.42 calculated as Cohen's d). Given the absence of any difference in hit rate for caffeine, the d' effect must result from subjects making fewer false alarms on caffeine.

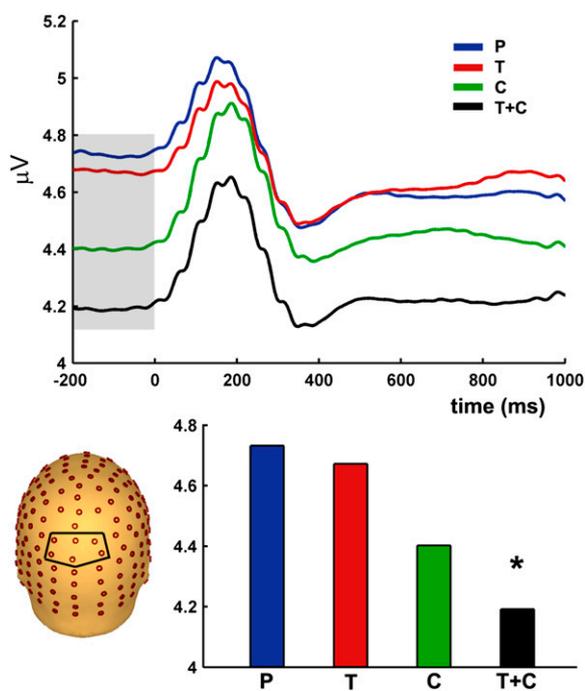


FIGURE 2 TSE waveforms at midline electrodes from which the baseline tonic alpha measure was derived (upper panel). Cue-left and cue-right trials are collapsed. Integrated amplitude over the baseline period for each treatment, with significant difference from placebo marked with an asterisk (lower panel). The electrodes from which tonic alpha measures were derived are marked on the 168-channel montage.

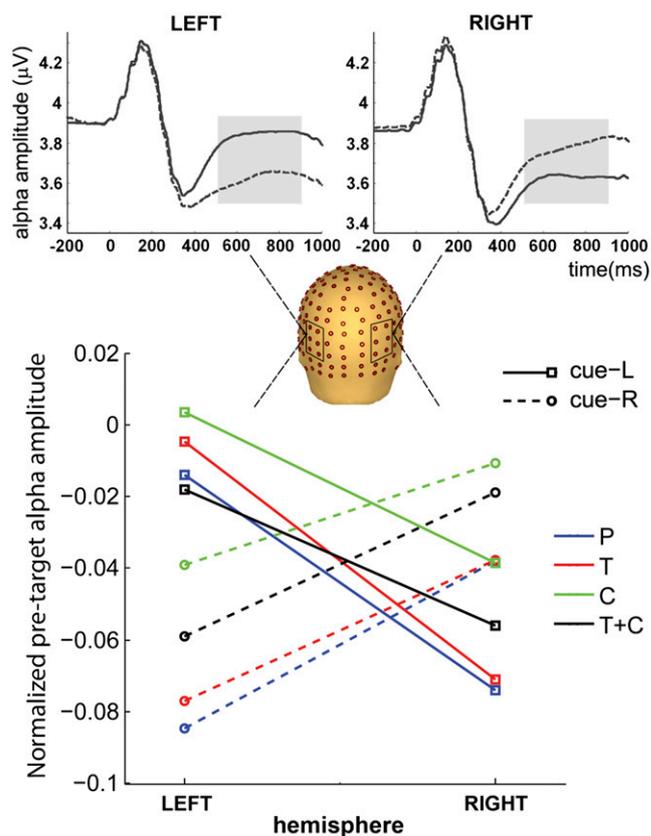


FIGURE 3 (Upper panel) TSE waveforms over left and right hemispheres, with cue-left (solid) and cue-right (dashed) superimposed, collapsed across treatment. The overall alpha-mediated spatial cueing effect is highlighted. Electrode sites for cueing effect measurement are marked on the montage. (Lower panel) Normalized alpha measures forming the dependent variable in tests for effects of treatment on the alpha cueing effect (P, placebo; T, L-theanine; C, caffeine; T+C, combined).

Tonic alpha amplitude was not found to decrease significantly on the lower dosage of L-theanine. This indicates that the effect is dose dependent because a drop was seen in both of our previous studies using a 250-mg dosage (18, M. Gomez-Ramirez, S. P. Kelly, J. L. Montesi, and J. J. Foxe, unpublished results). There was, however, a significant decrease in tonic alpha for the combined treatment. That this decrease marks a synergy between the 2 compounds is suggested by the numerical difference in the alpha decrease caused by L-theanine with and without caffeine (Fig. 2). That is, it seems unlikely that the greater decrease on the combined treatment is simply a linear sum of the decreases from each compound alone. Because only single dosages of each compound were tested, however, a fair degree of caution is appropriate in the interpretation of synergy at this juncture. This study marks the third finding of decreased alpha as a result of L-theanine ingestion (albeit a partial cause here) to date, demonstrating the reliability of the effect. At this point, the question of whether it translates to an improved functional brain state requires serious consideration. Should the finding of a decrease be received with positive connotations for health and/or mental capabilities?

In the 80 y since the discovery of alpha waves (24), alpha has been measured in almost any experimental situation and human population, with significant effects abounding, but with a complicated picture and quite disparate theoretical frameworks arising (25–26). A consistent principle appears to be that

stronger alpha infers positive functioning across individuals (27,28), whereas phasic changes within individuals reflect immediate stimulus processing and anticipatory enhancement and/or suppression, with a greater retinotopically specific decrease in alpha being predictive of better detection performance (21). The tonic depression of alpha during task performance over the day of testing, as observed here, is neither an individual trait nor a phasic event-related response but a lasting, tonic treatment effect, making it difficult to draw comparisons with such previous studies. The finding of **increased alpha on ingestion of theanine** has previously been taken to indicate **increased relaxation without increased drowsiness** (13). But this qualification appears tenuous in light of other observations of treatment-related increased alpha, e.g., during marijuana-induced euphoria (29). Can “good” and “bad” really be ascribed to increases and decreases in alpha, in whatever direction? Certainly, that **this treatment-related decrease in tonic alpha does not have negative implications is suggested, if not already by the fact that tea has been keenly, routinely consumed for centuries, by the concomitant facilitation in behavioral performance found here in terms of both hit rate and d' .**

Previous studies have reported a drop in absolute alpha power during resting with eyes open on ingestion of caffeine at higher dosages, e.g., 200 mg (30) and 400 mg (31). Although alpha amplitude was numerically lower on 50 mg of caffeine alone here, this did not reach significance ($P = 0.18$). From this, it is clear that alpha effects of both L-theanine and caffeine are dose dependent, demonstrating that full characterization of dose-response functions in future studies is called for.

Evidence of a synergistic relationship between L-theanine and caffeine has been presented in recent behavioral studies. Parnell et al. (32) reported improved speed and accuracy on an attention-switching task at 60 min and reduced susceptibility to distracting information during a memory task at both 60 and 90 min following ingestion of a combination of L-theanine and caffeine in the same dosages as used here. Haskell et al. (33) administered a large battery of cognitive tests before and after consumption of a drink containing either placebo, 250 mg of L-theanine, 150 mg of caffeine, or their combination. These authors found improvements in simple and numeric working memory RT, sentence verification accuracy, and alertness ratings for the combined treatment but not for either treatment alone. Using a similar crossover design but with a greater dosage of caffeine (250 mg) than L-theanine (200 mg), Rogers et al. (34) found that L-theanine tended to counteract the caffeine-induced rise in blood pressure but did not interact with caffeine-induced increases in either alertness or “jitteriness” on state anxiety scales. Although the measures examined in these investigations and our study are quite distinct in nature, an emerging possibility is that the presence of synergistic effects closely hinges on dosages. That is, it may be that theanine was not effective in augmenting the caffeine-induced effects in Rogers et al. (34) because these were present at a saturated level. In the present study, lower dosages were used, and **a significant drop in tonic alpha was observed for L-theanine and caffeine ingested together but not for either L-theanine or caffeine when ingested alone.** However, the absence of a significant difference between the caffeine-alone and combined treatments calls for caution in making strong claims of synergy at this point.

Similar to our previous visuospatial attention study (M. Gomez-Ramirez, S. P. Kelly, J. L. Montesi, and J. J. Foxe, unpublished results), we did not find any change in the alpha differential cueing effect for the L-theanine-alone treatment. However, **it is interesting that the cueing effect was found to be**

smaller on caffeine alone but not for the combined treatment.

This result was unexpected and thus will bear replication and further investigation. For now, it appears that within visual space, attentional biasing as indexed by alpha amplitude is not affected by L-theanine. In contrast, **the cued biasing of attention between sensory modalities does appear to be affected** (18). A tentative interpretation of the current pattern of results is that **L-theanine works to enhance the tonic apportionment of attentional resources to the visual modality and does so to a significant degree when a large dosage is ingested by itself or in combination with caffeine when a smaller dosage is ingested.**

Other articles in this supplement include references (35–44).

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