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The effects of L-theanine, caffeine and their

combination on cognition and mood

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Abstract

L-Theanine is an amino acid found nahirally in tea. Despite the common consumption of t,-theanine, predominantly in combination with caffeine in the form of tea, only one shidy to date has examined the cognitive effects of this substance alone, and none have examined its effects when combined with caffeine. The present randomised, placebo-controlled, double-blind, balanced crossover study investigated the acute cognitive and mood effects of t,-theanine (250 mg), and caffeine (150 mg), in isolation and in combination. Salivary caffeine levels were co-monitored. t,-Theauine increased `headache' ratings and decreased coirect serial seven subtractions. Caffeine led to faster digit vigilance reaction time, improved Rapid Visual Information Processing (RVIP) accuracy and attenuated increases in self-reported `mental fatigue'. In addition to improving RVIP accuracy and `mental fatigue' ratings, the combination also led to faster simple reaction time, faster numeric working memory reaction time and improved sentence verification accuuacy. `Headache' and `tired' ratings were reduced and `alert' ratings increased. There was also a significant positive caffeine x t,-theanine interaction on delayed word recognition reaction time. These results suggest that beverages containing L-theanine and caffeine may have a different pharmacological profile to those containing caffeine alone.
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Keywords: r~-Theanine; Caffeine; Tea; Cognition; Mood; Memory; Attention; Humans

l . Introduction

Behavioural effects of caffeine, particularly in the form of
caffeinated coffee, have received considerable attention in the
literature. Numerous studies have highlighted the beneficial effects of caffeine on cognition and mood (see Smith, 2002).
The most commonly reported being increases in ratings of

`alertness' (Rogers et al., 2003), faster reaction times, and improved sustained attention (Lieberrnan et, a1., 1987; Richardson et a1., 1995). A detailed description of the pharmacological actions of caffeine is beyond the scope of this paper, the mechanisms underlying these effects have, however, been discussed in depth elsewhere (for review see Fredholm et al., 1999). Although caffeine is rarely consumed in isolation, far less is knowl~ about the behavioural effects of caffeine when combined with other concomitant phytonuti~-

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eats. Of particular interest are the effects of caffeine when consumed in the form of tea, given that, with the exception of water, it is the most widely consumed beverage in the world (Gilbert, 1984).
Studies that have considered effects of tea have found that, although the majority of effects can be explained by caffeine, some differences exist between tea and coffee, even when the caffeine level is matched. Quinlan et al. (1997} found that tea, containing 100 tng caffeine, had significantly greater effects than coffee with a matched caffeine level, in raising skin temperature. Hindmarch et al. (2000} also found that tea significantly increased critical flicker fusion threshold when compared with coffee, despite both beverages containing 75 mg caffeine. Coffee also significantly speeded recognition reaction time over that of tea at the same dose. Steptoe et al. (2007) considered the effects of chronic tea administration, containing 72 mg caffeine, on acute stress responses as compared to a control matched for caffeine level. They found that tea was able to reduce platelet activation and cortisol evels in response to stress, as well as il~crease `relaxation' ratings relative to control.

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The finding of decreased cortisol levels is particularly
interesting, as caffeine has been shown to increase cortisol
levels, especially in response to stress (Lovallo et a1., 2006).
This suggests that components within tea were achially able to

produce an opposing effect to that seen with caffeine.
A possible candidate for the modulation of caffeine effects, evinced in the form of tea, is the amino acid, L-theaniue ('y-glutamylethylamide). Animal studies have shown thatL-theaniue is able to inhibit the stinmlation produced by caffeine, as evaluated by EEG (Kakuda et al., 2000), and measures of spontaneous activity (Kimura and Mttrata, 1971). In line with these findings, L-theaniue has been used historically as a relaxing agent. However, its pharmacology is relatively unknown and human research in this area is by no means conclusive. Lu et al.

(2004} studied the subjective mood effects of L-theaniue and found that 200 tug L-theaniue was able to increase `tranquil' ratings, as measured by the `ri'auquil-troubled' item of the Bond-Lader visual analogue scales (Bond and Lacier, 1974). However, this finding was oltly evident in rested participants and was not replicated when participants were tinder conditions of increased anxiety. Conversely, Kimura et al. (2007) found reduced heart rate and salivary IgA responses to acute stress following 200 mg L-theaniue. In addition, `state anxiety' (Spielberger, 1977) and subjective perceived `stress' ratings were also reduced following L-theaniue as compared to placebo„Similarly, Kobayashi et al.

(1998} found that 200 mg L-theaniue, but not 50 mg, led to increased alpha (tx) waves when administered to resting

participants, which the authors suggest is indicative of relaxation without drowsiness. However, Gomez-Ramirez et al. (2007} found evidence of a decrease in alpha activity following 250 mg L-theaniue when measured during performance of a highly demanding attention task. This study also represents the only investigation to date of cognitive effects of L-theaniue in humans, and this decrease iii alpha activity was associated with a slowing of reaction time on ati auditory attention task.
Clearly further research is needed to explore the cognitive effects of L-theaniue and to clarify some of the mood effects. Given the evidence from animal studies for an interaction between caffeine arid L-theaniue, and the fact that the vast majority of 1;-theaniue consumption is iti the form of tea, it is important to assess the effects of L-theaniue alone and in combination with caffeine. The current randomised, placebo-controlled, double-blind, balanced crossover study investigated the cognitive and mood effects of administration of the two agents both alone [L-theaniue (250 mg), caffeine (150 mg)] and in combination (250 mg/150 mg). The tasks selected included attentional tasks as well as specific semantic memory and semantic reasoning tasks, which are known to be sensitive to caffeine (e.g. Haskell et al., 2005; Wa1'burton, 1995; Smith et a1., 1994, 1999). Additional secondary memory tasks were also included, which although not typically sensitive to caffeine, have been shown to be improved by caffeine when combined in the form of guarana (Haskell et al., 200'7). Furthermore, this extensive range of tasks also allowed a cognitive profile for L-theaniue to be produced, which is essential given the lack of evidence with regards the effects of th1S SnbStalrCe.

2. Methods

2.1. Initial screening

Prior to participation in the study volunteers signed an informed consent form and completed a medical health questionnaire. All participants reported that they were in good health and free from social drugs and medication with the exception of the contraceptive pill. Habitual smokers were excluded from the study.

2.2. Participants

Participants were informed that the study investigated the cognitive and mood effects of a commercially available fnut drink containing active components (one of which may be caffeine). Twenty-four participants completed the experiment (9 male and 15 female, mean age 21.3 years, S.E.M. 0.83, range 18-34 years). All were undergraduate volunteers. Participants abstained from caffeine and alcohol for a minimum of 12 h prior to the first testing session and throughout the morning until the final testing session was completed. The study was approved by dre Northumbria University Division of Psychology 1?tlucs Committee, and was carried out in accordance with the Declaration of Helsinki.

2.3. Sali>>ary caffeine lerels

Saliva samples were obtained using salivettes (Sarstedt, Leicester, UK). Samples were taken immediately prior to baseline assessment in order to confirm compliance to overnight abstinence and immediately prior to both post-treatment assessments to confirm effective caffeine absor(~tion. The saliva samples were inmmediately frozen at -20 °C until thawing for in-house batch analysis using the Emit system (Syva, Palo Alto, USA). This is an enzyme immunoassay intended to measure caffeine as a metabolite and is based on competition for antibody binding sites between caffeine and an enzyme labelled ding.

2.4. Assessment

A tailored version of fire Cognitive Drug Research battery (CDR Ltd., Goring-on-Thames, UK) was used. The CDR computerised assessment battery lras been used in lnmdreds of Etuopean and North American drug trials, and has been shown to be sensitive to acute cognitive improvements as well as impairments with a wide variety of substances (e.g. Scholey et al., 1999; Kennedy et al., 2002, 2003) including caffeine (Scholey and Kennedy, 2004; Haskell et al, 2005).
The selection of computer-controlled tasks from the system was adminis-tered with parallel forms of the tests being presented at each testing session. Presentation was via laptop computers. All responses were recorded via two-button (YeslNo) response boxes with the exception of the written word recall task. A full description of the tasks used can be found in Kennedy et al. (2003). Additionally, a logical reasoning task was included as well as a sentence verification task and serial subtractions. Mood scales employed were the Bond-Lader visual analogue scales (Bond and Lader, 1974) and the Caffeine Research Visual Analogue Scales (CRVAS) (described in Haskell et al., 2005).

2.5. Treatments

Participants received four drinks containing: (1) 0 mg caffeine plus 0 mg t.- tlreanine (placebo); (2) 150 mg of caffeine; (3) 250 mg t.-theaniue and (4) 150 mg caffeine plus 250 mgt,-theaniue on separate occasions. In each case the h~eatment was presented in a 250 ml modified Peach Lite Lipton Ice Tea drink. During initial preparation all tea powder (including t,-theaniue and caffeine) was removed from the drink and the sweetener levels adjusted to mask the bitter taste of klre high.dose of added caffeine so that no discernible taste difference could be detected between the drinks. The drink also contained the following: trisodium citrate; peach flavour; peach juice; malic acid; aspartame; acesulfame K and ascorbic acid. Ten minutes was allowed for drink consumption. These drinks were prepared off-site and assigned a treatment code by a disinterested thh-d party.

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2.6. Procedure

Each participant was required to attend a total of 5 study days that were conducted 7 days apart to ensure a sufficient wash out between conditions. Testing took place in a suite of laboratories wiUr participants visually isolated

from each other. On arrival at Ureir first session on Ure first day, participants were randomly allocated to a treatment regime using a Latin square design that counterbalanced the order of treatments across dre 4 active days of the study. The first day involved completion of the test battery four times in order to control for practice effects and to allow familiarisation with Ure test battery and procedure on subsequent visits. The practice day data were not included in any analyses.
Each of the four active study days comprised tlu-ee identical testing sessions. The first was a pre-dose testing session; which established baseline performance for that day, the second took place 30 min post-drink and Ure final session took place 90 min post-drink.
Each testing session lasted approximately 30 min and comprised producing a saliva sample; completion of the CDR test battey, a sentence verification task, serial subtractions (threes and sevens) and visual analogue mood scales.

2.7. Statistics

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Salivary Caffeine

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Caffeine [F(1, 21)=113, p<0.0001]

Placebo Caff L-they Caff+L-thea

Fig. 1. Mean change from baseline salivary caffeine levels are presented following placebo. 150 mg caffeine, 250 mg t,-theanine, and a combination of 150 mg caffeine plus 250 mg r.-theanine, with more positive values repre-senting higher levels. Significant reatment effects compared with placebo are indicated ~~""'(p < 0.0001). Main effect of caffeine from ANOVA is indicated.

3.3. Post-treatment CDR scares

Prior to the primary statistical analysis, separate, one way, repeated mea-sures ANOVAs of pre-dose baseline data were conducted to ascertain any chance baseline differences in performance across study days prior to dte

treannents.

Scores on the individual task outcomes were analysed as `change from baseline' using Minitab 14.0.1.
A 2 x 2 x 2 repeated measures ANOVA (General Linear Model) was carried out on the `change from baseline' data, wiUt terms fitted to the model for caffeine (present, absent); r.-Ureanine (present, absent) and assessment (30 min, 90 min). This analysis adequately describes Ure main effect of caffeine across the two caffeine containing drinks, Ute main effect of t.-Uteanine across the two t,-Ureanine containing drinks, and any interaction between the two, but does not explore the effects of the individual drinks in comparison to placebo. Therefore, any meastu~es that generated a significant main or interaction effect were fitrUter explored using Student's paired t-tests comparing the relevant active U~eatment(s) to placebo. To ensure the overall Type I error protection level all testing was two-tailed. In addition, effect sizes were calculated using Cohen's d.

3. Results

Only those meast>res that generated significant main, or interaction effects, are reported below.

3.3.1. Simple reaction time
There was a significant main effect of caffeine on simple reaction time [F(1, 23) = 5.67, p < 0.05]. However, compar-isons of both of the individual caffeine bearing chinks to placebo showed that this reached significance only following caffeine plus 1.-theanine [t(23) = 2.67, p < 0.05, d = 0.7], see Fig. 2a.

3.3.2. Digit vigila.n.ce reaction time
Digit vigilance reaction time showed a significant main effect of caffeine [F(1, 23) = 6.67, p < 0.05]. Comparisons of both caffeine bearing treatments to placebo revealed that reaction time was significantly faster only following caffeine alone [t(23) = 2.33, p < 0.05, d = 0.7], see Fig. 2b.
3.1. Salivary caffeine levels

Salivary analysis confirmed compliance with overnight abstinence, mean baseline values were 0.42 l.t,g/ml (levels just below 1 ~ghnl have been reported for overnight caffeine abstinence-Evens and Griffiths, 1999). Two datasets from time points other than baseline were unusable and were excluded from any analyses. Analysis of post-treatment salivary caffeine levels revealed a main effect of caffeine [F(1, 21) = 113, p < 0.0001], with sigtuficantly higher salivary caffeine levels following caffeine administration [t(21) = 9.3Q p < 0.0001, d = 2.5] and following the combination [t(21) = 8.28, p < 0.0001, d = 2.2], see Fig. 1.

3.3.3. Rapid Visual Information P~ocessirag (RVIP)
There was a significant main effect of caffeine ou accuracy of the RVIP task [F(1, 23) = 28.31, p < 0.0001]. This emerged as a significant improvement following both the caffeine drink [t(23) = 3.23, p < 0.005, d = 0.9] and the caffeine/1.-theanine combination [t(23) = 4.35, p < 0.001, d = 1.0], see Fig. 2c.

3.3.4. Spatial memory accuracy (SI)
Due to significant baseline differences in spatial working memory baseline scores were included as a covariate in an ANCOVA performed on this measure. No significant differ-ences remained following this analysis.

3.2. Baseline scores

Mean pre-dose baseline scores and change from baseline scores, for each condition on each outcome measure are

presented in Tables 1 and 2. There were significant baseline differences in accuracy of spatial memory (F(3, 69) = 2.82, p < 0.05) and ratings of `content' jF(3, 69) = 3.00, p < 0.05].

3.3.5. Numeric wanting mernary reaction time
Numeric working reaction time showed a significant main effect of caffeine [F(1, 23) = 7.39, p < 0.05]. t-Tests compar-ing both caffeinated treatments to placebo revealed that this effect was restricted to a significant improvement following caffeine plus 1.-theanine [t(23) = 2.26, p < 0.05, d = 0.5], see Fig. 2d.

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cturent study. It is unforhmate that no such record was made in the Gomez-Ramirez et al. (2007) study, as this would have allowed comparison between the two.
Caffeile alone improved speed of digit vigilance reaction tithe (Fig. 2b) and accuracy of Rapid Visual Information Processing (see Fig. 2c), and attenuated increases in self-reported `mental fatigue' ratings. The improvements to digit vigilance reaction time and `mental fatigue' ratings replicate those reported previously for 150 mg caffeine, using the same battery in habitual consumers and habitual non-consumers of caffeine (Haskell et al., 2005). It has been suggested that caffeine merely reverses the negative effects of caffeuie withdrawal (Rogers et al., 2003) so, given that the participants in the current study were overnight caffeine withdrawn (as confirmed by analysis of salivary caffeine levels), it is unfortunate that no record was taken of habitual caffeine use, as this would have added to the debate in this area and also allowed comparison with the findings of Haskell et al. (2005} of similar esponses to caffeine in consumers and non-consumers of caffeine. Of particular interest in the current st<uly would be a record of habitual caffeine consumption, with specific reference to the source of caffeine, as this would allow exploration of any differential effects of caffeine in relation to regular caffeine source. It would also be interesting in the case of r:-theanine to establish whether these effects differ with regard to habitual tea use. Related to habitual consumption is the possibility that, despite the removal of all tea powder, aplacebo response to iced tea may have been elicited in some participants and not iu others as a result of previous use.
Turning to the r.-theanine-caffeine combination, there were a number of measures that were sensitive to this treatment. Simple reaction time (Fig. 2a), accuracy of RVIP (Fig. 2c), numeric working memory reaction time (Fig. 2d), delayed word recognition reaction time (Fig. 2f) and accuracy of sentence verification (Fig. 2e) were all improved by the combination. In

addition, Bond-Lader `alert' ratings (Fig. 3a) were increased, `tined' (Fig. 3b) and `mental' fatigue' ratings (Fig. 3c) were
decreased and `headache' ratings were reduced (Fig. 3d). The only effect of caffeine not evident following the combination was an inprovement to digit vigilance reaction time. Given that r,-theanine isa `relaxant,' and the effects of caffeine are usually attributed to its `stimulant' properties, it is not clear why the addition of r;-theanine should ameliorate the effects of caffeine. However, itis interesting to note, that the only task to show an attenuation of the effects of caffeine when combined with z-theanine, was a sustained attention task that has previously been shown to be extremely sensitive to caffeine. In contrast, greater potentiation was observed on memory measures, which tend to be unaffected by caffeine on the whole.
The greater effects of the combination than caffeine alone on increased `alert' ratings and reduced `tired' ratings contradict those of Kakuda et al. (2000) who reported an inhibitory effect of i,-theanine on caffeine's stimulatory properties iu rats. However, the doses used are far lower than those employed previously, and it is not clear whether comparable effects would be seen in humans. iu the latter study. Furthermore, itmay be simplistic to consider psychopharmacological effects in terms

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of straightforward stimulant or depressant effects. Firstly such effects are dose-dependent, classic CNS depressants such as alcohol may have stimulant effects at low doses (e.g. Scholey and Fowles, 2002). Similarly, caffeine at very high doses (outside the range used here) inhibits cognitive function and we have some evidence of functional impairment from very low

doses (Haskell et al., in press). Thus mutual behavioural antagonism between depressant and stinnilant drugs may be dose-dependent (e.g. Smith et al., 2003; Mackay et al., 2002). In addition, even when such effects manifest themselves at the behavioural level one should not simply assume that the two substances hare common neurochemicaL targets.
In the context of the current study the mechanisms underlying the reported effects are not known. At the neurochemical level, both caffeine and t,-theanine have been shown to, directly or indirectly, affect several neurotransmitter systems. Common targets may include dopamine, serotonin, glutamate and GABA. However, to the best of our knowledge, the effects of r.-theanine and caffeine iu combination have not been shulied at the receptor level: There may be psychophar-macological interactions between caffeine and r.-theanine, but without further work delineating the mechanisms of r.- theauine's psychoactive properties this remains a matter of conjecttu~e. It is clear from analysis of salivary caffeine levels that the reason for the difference in effects of caffeine and the combination, in favour of the latter, are not as a result of increased caffeine absorption. However, the greater effect size for increased salivary caffeine following caffeine may be indicative of greater absorption of caffeine froth exh~acellular fluids following the combination. Itis also interesting to note that, with the exception of reduced `headache' ratings, the effects of the caffeine-t,-theanine combination and caffeine in isolation are all apparent at both 30 and 90 min post-administration. °

The levels of L-theanine and caffeine used here are higher than those found in tea beverages, which are typically in the region of 40 mg caffeine and 20 mg L-theanine. In this initial study it was felt that the use of known psychoactive closes was important in order to establish a netuocognitive profile for L-theanine and to examine effects of a caffeine-r.-theanine combination. Further studies should be aimed at a full dose-

ranging study for t,-theanine, particularly as at least one study has reported mild psychostinrulant effects in rats following lower rather than higher doses of L-theanine (Kakuda et al., 2000). Additionally, the next stage of studies into r.-theanir~e-caffeine combinations hould include examination of the

effects of everyday doses both in isolation and in combination at levels and ratios found iu real tea beverages. It is also clear that teas contain a host of potentially psychoactive ingredients, which, as well as L-theanine and caffeine, include catechins, tannins and saponins amongst others. Additionally, green tea has been reported to have anti-cholinesterase properties (Okello et al., 2004), although the components responsible for this property are at present unknown.
Further research should examine the effects of L-theanine on behaviour, ou its own and iu combination with the other components of tea.

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