Review

Green tea effects on cognition, mood and human brain function: A systematic review

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ARTICLE INFO

ABSTRACT

Background: Green tea (*Camellia sinensis*) is a beverage consumed for thousands of years. Numerous claims about the benefits of its consumption were stated and investigated. As green tea is experiencing a surge in popularity in Western culture and as millions of people all over the world drink it every day, it is relevant to understand its effects on the human brain.

Purpose: To assess the current state of knowledge in the literature regarding the effects of green tea or green tea extracts, L-theanine and epigallocatechin gallate both components of green tea—on general neuropsychology, on the sub-category cognition and on brain functions in humans.

Methods: We systematically searched on PubMed database and selected studies by predefined eligibility criteria. We then assessed their quality and extracted data. We structured our effort according to the PRISMA statement.

Outcome: We reviewed and assessed 21 studies, 4 of which were randomised controlled trials, 12 cross-over studies (both assessed with an adapted version of the DELPHI-list), 4 were cross-sectional studies and one was a cohort study (both assessed with an adapted version of the Newcastle–Ottawa assessment scale). The average study quality as appraised by means of the DELPHI-list was good (8.06/9); the studies evaluated with the Newcastle–Ottawa-scale were also good (6.7/9).

Conclusions: The reviewed studies presented evidence that green tea influences psychopathological symptoms (*e.g.* reduction of anxiety), cognition (*e.g.* benefits in memory and attention) and brain function (*e.g.* activation of working memory seen in functional MRI). The effects of green tea cannot be attributed to a single constituent of the beverage. This is exemplified in the finding that beneficial green tea effects on cognition are observed under the combined influence of both caffeine and L-theanine, whereas separate administration of either substance was found to have a lesser impact.

Introduction

Camellia sinensis, commonly known as green tea, has a long history in human culture and it has been considered to have medical properties for many years. There has recently been a great surge of interest in the health benefits of green tea; this is at least in part due to the effect of increasing consumption of green tea in Western countries. A trial in rats claims that polyphenols that are specific to green tea might provide functional neuroprotection in Parkinson's disease (Guo et al., 2007). Yet
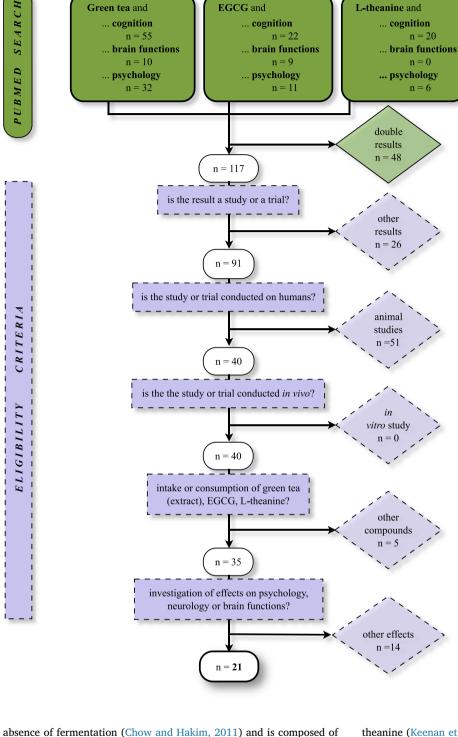
scientific interest in the medical qualities of green tea goes beyond neurodegenerative diseases, as reported in animal studies, showing that green tea polyphenols inhibited the growth of bladder tumour cells (Chen et al., 2004). Moreover, there is evidence that green tea acts as an antiviral agent in HIV-infection, although it is still unclear how these findings should be applied to current therapy (Nance and Shearer, 2003). Pastore and Fratellone have reviewed the broad spectrum of known or suspected effects of green tea (Pastore and Fratellone, 2006).

Green tea is prepared from steamed leaves of *Camellia sinensis* in

Fig. 1. Flowchart of the selection procedure.

PUBMED SEARCH

Green tea and
... cognition
n = 55
... brain functions
n = 10
... psychology
n = 32

EGCG and
... cognition
n = 22
... brain functions
n = 9
... psychology
n = 11

L-theanine and
... cognition
n = 20
... brain functions
n = 0
... psychology
n = 6

double results
n = 48

n = 117

is the result a study or a trial?

other results
n = 26

n = 91

is the study or trial conducted on humans?

animal studies
n = 51

n = 40

is the the study or trial conducted *in vivo*?

in vitro study
n = 0

n = 40

intake or consumption of green tea (extract), EGCG, L-theanine?

other compounds
n = 5

n = 35

investigation of effects on psychology, neurology or brain functions?

other effects
n = 14

n = **21**

ELIGIBILITY CRITERIA

absence of fermentation (Chow and Hakim, 2011) and is composed of many substances: most importantly catechins (30–42% of solid extract weight), of which epigallocatechin gallate (EGCG) is the most abundant (65%)(Nagle et al., 2006) (Scholey et al., 2012), followed by theanine (4–6%) and caffeine (3–4%)(Chow and Hakim, 2011). Black tea contains considerably lower amounts of non-oxidised catechins as it is produced by allowing enzymatic oxidation to occur in harvested leaves of *Camellia sinensis,* resulting in fewer catechins (3–10%) due to the formation of thearubigins and theaflavins (12–18% and 3–6% respectively) (Chow and Hakim, 2011). It is noteworthy that the addition of milk—as is customary in black tea–can decrease both the antioxidant qualities of polyphenols (Bourassa et al., 2013) and—in elevated quantities (more than 50 ml in a 200 ml cup)—the concentration of L-

theanine (Keenan et al., 2011).

The focus of the present review is on the effects of Epigallocatechin gallate (EGCG) and theanine, as *Camellia sinensis* is the main dietary source of both EGCG (Borgwardt et al., 2012) and L-theanine (Scheid et al., 2012). In fact, EGCG possesses anti-inflammatory and antioxidant qualities (Scapagnini et al., 2011). Several animal studies suggested that EGCG can pass the blood-brain barrier (Lin et al., 2007; Suganuma et al., 1998), whereas zini et al. could not trace detectable amounts of EGCG in the cerebrospinal fluid of multiple sclerosis patients after consumption of green tea (Zini et al., 2006). More recently, an *in vitro* study by Faria et al. (2011) showed that the human brain capillary endothelial cells forming the blood-brain barrier (BBB) permit the passage of catechins and epicatechins. The bioavailability of EGCG and

other green tea catechins appears to be less marginal than previously proposed if the calculation includes metabolites derived from colonic microflora: the calculated bioavailability then increases from 4% (just EGCG) to 39% (EGCG including metabolites) (Del Rio et al., 2010). The same study found that a peak plasma concentration 0.08 μmol/l of EGCG was observed at 1.4 h after oral administration of 11.8 mg EGCG to humans.

On the other hand, ʟ-Theanine reached in human volunteers a peak plasma concentration of 26.5 μmol/l at 0.8 hours after oral intake of 250 ml of green tea (Scheid et al., 2012). ʟ-Theanine passes through the BBB, interacts with the glutamine transporter and inhibits neural incorporation of glutamine (Kakuda, 2011).

Although several implications of the neuro-modulating properties of green tea have already been investigated, no previous studies reviewed green tea's impact on the human brain. Thus, the aim of this systematic review was to assess the effects of green tea on cognition and human brain functions.

Material and methods

Eligibility criteria

We defined five eligibility criteria for our search results: (1) The search result was a study or a clinical trial. (2) The search result had an *in vivo* design. (3) The search result was a study conducted on humans. (4) The search result featured an intervention with and without exposure to either green tea (extract), EGCG, ʟ-theanine or combinations thereof. (5) The search result contained outcomes pertaining to the fields of brain functions, neurology or neuropsychology. Criteria (1–3) were set in place to assure that an eligible search result would provide data that could easily be translated to clinical or nutritional questions. Criterion (4) was devised to assure that search results contained the desired green tea components. Finally, criterion (5) guaranteed that the outcome was in the predefined fields of interest.

Keywords

We selected seven key words to best cover and represent the different components of our initial question: green tea, epigallocatechin gallate, ʟ-theanine, cognition, cognitive functioning, brain functions, psychology. The first three key words covered the desired intervention or exposure; the other four key words related to the desired outcome. "Green tea effect" was simplified for this purpose and assumed to be the effect of green tea or of its two main defining components.

Information source

We chose the online database PubMed as sole information source. We limited ourselves to English language results and considered results regardless of year or publication status. The search was conducted from March 25th 2013 to January 19th 2015.

Search strategy

We systematically searched our information source for our key words. We used all the permutations of intervention-keywords with outcome-keywords. The hits under "cognitive functioning" were added to those for "cognition" in Fig. 1 for the sake of simplicity. We then screened the results for duplicates and eligibility criteria. The extract of this process was included in our review.

Data extraction and quality assessment

This systematic review was structured according to the PRISMA checklist 5. One reviewer (E.M.) extracted the data.

Firstly, we focused on five categories at the level of the study:

- *Participant* characteristics, number, gender, mean age and—if present—other specific defining factors.
- *Intervention characteristics*, which means substances that we had previously searched for and substances that were inextricably linked to them by the study design—*e.g.* caffeine—both with dosages.
- *Control* characteristics, which documented the presence or absence of controls—most notably placebo.
- *Study Design* that was explicitly stated in the respective study.
- Finally, only *outcome measures* were listed that could possibly produce an outcome pre-specified in eligibility criterion (5). If there were significant data, these were highlighted.

When extracting data from the observational studies, we substituted the term "*Intervention*" for the more accurate term "*Exposure*" as the substances in question were no longer administered under standard conditions, yet consumed habitually. We also replaced the category "*Control*" with the factor "*Time*" to indicate when a result was reported and the period of time for which it was monitored if there was a follow-up. The other data extraction categories remained the same.

Secondly, we extracted the outcome. We focussed on four aspects of the outcome of each study:

- Cardiovascular effects,
- Neuropsychological effects,
- Neurocognitive effects
- Brain functions.

These data extraction groups were the same for all studies regardless of their design.

Thirdly, we conducted quality assessments of the 21 studies to systematically assess their most important biases and weaknesses. We chose the DELPHI list (Verhagen et al., 1998) to rate the experimental trials and the Newcastle–Ottawa scale (De la Torre et al., 2014) to evaluate the quality of the observational studies. However, the tools had to be adapted for certain study designs: as the DELPHI list was specifically designed for randomised controlled trials, some adjustments (de Morton, 2009) had to be made to assess the quality of repeated measures designs.

A similar difficulty arose with the Newcastle–Ottawa scale, which was originally conceived to rate cohort studies and case-control studies; therefore, we had to make some adaptations for cross-sectional studies. The Appendix contains full details of the *quality assessment tools and full assessment*.

Types of investigations

The trials with a crossover design—also known as ‚within subject 'or ‚repeated measures' design—examined the various effects of green tea extract, EGCG or ʟ-theanine on healthy subjects. For this purpose the test subjects underwent both placebo and 'treatment' conditions over the entire course of the trial. Between the testing dates a wash-out period was observed, for the participants to return to baseline values. The (first) testing was performed within 90 minutes after intake. To correct for order effects (counter-) balancing according to a Latin Square design was applied. The methods used in the scrutinised body of work are summarized in Table 1.

Results

Study selection

We identified 165 publications—117 after eliminating 48 duplicates—and proceeded to screen these results for eligibility using the inclusion criteria: (1) We selected only studies or trials (26 reviews/ essays/ book chapters were excluded); (2) The subjects had to be human (51 animal studies were excluded); (3) The study had to be *in vivo*; there

Table 1
Screening criteria: randomized, placebo-controlled studies.

A) *Healthy volunteers, acute green tea effects*

	Participants	Intervention	Study design	Outcome measures
Schmidt et al. (2014)	12 (12 men, mean age: 24.1 years)	**Green tea extract** (13.75 g or 27.5 g): 1 g corresponding to 5.5 g green tea leaves; calculated contents: EGCG (4700 mg or 9400 mg), L-theanine (400 mg or 800 mg), caffeine (1350 mg or 2700 mg)	Double-blind, controlled, counterbalanced within- subject trial	Working memory n-back task, **fMRI**
Borgwardt et al. (2012)	12 (12 men, mean age: 24.1 years)	**Green tea extract** (13.75 g or 27.5 g): 1 g corresponding to 5.5 g green tea leaves; calculated contents: EGCG (4700 mg or 9400 mg), L-theanine (400 mg or 800 mg), caffeine (1350 mg or 2700 mg)	Double-blind, controlled, counterbalanced within-subject trial	Working memory n-back task, **fMRI**
Scholey et al. (2012)	31 (12 men, mean age: 27.7 years)	**Green tea extract** (caffeine free) of which 94% EGCG (300 mg) and 6% vitamin C	Double-blind, controlled crossover trial	**EEG, VAS**
Wightman et al. (2012)	27 (11 men, mean age: 22 years)	**EGCG** (135 mg or 270 mg)	Double-blind, controlled, balanced crossover trial	**Near infrared spectroscopy**, odd-ball reaction time, serial subtractions, RVIP, Stroop task, VAS
Ota et al. (2014)	14 (7 men, mean age: 31.0 years)	**L-theanine** (200 mg, 400 mg, 600 mg)	Double-blind, controlled, counterbalanced cross-over trial	**Prepulse inhibition test**
Yoto et al. (2012)	16 (8 men, mean age: 22.8 years)	**L-theanine** (200 mg) or caffeine	Randomised, controlled, crossover trial	Stress-load task, **physiological measurement, POMS**, VAS
Giesbrecht et al. (2010)	44 (16 men, mean age: 21.2 years)	**L-theanine** (97 mg) and **caffeine** (40 mg)	Double-blind, randomised, controlled, counterbalanced within-subject trial	Physiological measurement, choice-reaction-time task, visual-search task, egocentric mental-rotation task, **attention-switching-task, task demand rating scale**, VAS
Einöther et al. (2010)	29 (11 men, mean age: 30.6 years)	**L-theanine** (97 mg) and **caffeine** (40 mg)	Double-blind, randomised, controlled, crossover trial	Intersensory attention task, **switch task**, VAS
Owen et al. (2008)	27 (14 men, mean age: 28.3 years)	**L-theanine** (100 mg) and **caffeine** (50 mg)	Double-blind, randomised, controlled, crossover trial	Word recognition, RVIP, CFFT, **Attention-switching task**, VAS
Kelly et al. (2008)	16 (11 men, mean age: 27.5 years)	**L-theanine** (100mg) or **L-theanine** (100mg) and **caffeine** (50 mg)	controlled, balanced, repeated-measures trial	EEG, neurocognitive test
Haskell et al. (2008)	24 (9 men, mean age: 21.3 years)	**L-theanine** (250 mg) or **L-theanine** (250 mg) and **caffeine** (150 mg)	Double-blind, randomised, controlled, balanced crossover trial	**CDR: simple reaction time**, digit vigilance reaction time, **RVIP**, spatial memory accuracy, **numeric working memory reaction time, delayed word recognition reaction time, sentence verification accuracy, serial sevens subtraction task, VAS, CRVAS**
Kimura et al. (2007)	12 (12 men, mean age: 21.5 years)	**L-theanine** (200 mg)	Double-blind, controlled, counterbalanced crossover trial	**Physiological measurement, VAS, state-trait anxiety inventory**

CFFT, critical flicker fusion threshold; EEG, electroencephalography; EGCG, epigallocatechin gallate; fMRI, functional magnetic resonance imaging; POMS, profile of mood states; RVIP, rapid visual information processing; VAS, visual analogue scale.

B) *Patients, non-acute green tea effects*

	Participants	Intervention	Study design	Outcome measures
De la Torre et al. (2014)	29 (15 male, patients with Down Syndrome, mean age: 21.3 years)	**EGCG** (360 mg)* **caffeine** (25 mg) *9 mg/kg/d	Double-blind randomised, controlled pilot study (12 weeks)	CANTAB: **psychomotor speed**, attention, **episodic memory, executive functions**, visuomotor precision. Parents/ caregivers: scales of functional ability in daily living, adaptive behaviour, **QLS**
Park et al. (2011)	91 (25 men 40–75 years) mild cognitive impairment (MMSE-K 21–26)	**Green tea extract** (360 mg) and **L-theanine** (60 mg), twice a day	Double-blind, controlled trial (16 weeks)	MMSE-K, GDS, **Rey-Kim memory test, Stroop colour-word reading test, EEG**
Ritsner et al. (2011)	60 (48 men, mean: 36.5 years) schizophrenia or schizo-affective disorder	**L-theanine** (400 mg) and antipsychotic medication	Double-blind, randomised, controlled (2-Centre) trial (8 weeks)	CGI-S, **PANSS**, CDSS, **HARS**, CANTAB, GAF, ESRS, QLS, Q-LES-Q-18
Brown et al.	100 (100 men, age 40–65	**EGCG** (800 mg)	Double-blind, randomized, parallel	**UWIST mood adjective checklist, physiological**

CANTAB: Cambridge neuropsychological test automated battery; CDSS, Calgary depression scale for schizophrenia; CGI-S, clinical global impressions-severity of illness scale; EGCG, epigallocatechin gallate; EEG, electroencephalography; ESRS, extrapyramidal symptom rating scale; GAF, global assessment of functioning; GDS, global deterioration scale; HARS, Hamilton anxiety rating scale; MMSE-K, mini mental scale examination-Korean; PANSS, positive and negative syndrome scale; Q-LES-Q-18, quality of life enjoyment and satisfaction questionnaire- abbreviated version, QLS, quality of life scale.

Table 1 (continued)

B) Patients, non-acute green tea effects

	Participants	Intervention	Study design	Outcome measures	measurements
(2009)	years) Obesity with BMI > 28 and <38 kg/m²	Green tea consumption (and other tea and coffee)	design (matched for insulin resistance and age) trial (8 weeks)		Survey, long-term care insurance certification
Tomata et al. (2012)	23,091 (≥65 years)	Green tea consumption (and general tea consumption)	2006 3 year follow-up	Prospective cohort study	Questionnaire, interview, MMSE, attention-, memory-, executive function-, information processing speed-score
Feng et al. (2010)	716 (≥55 years mean: 64.5 years)	Green tea consumption (and general tea consumption)	?	Cross sectional study set in the Singapore Longitudinal Ageing Studies	
Hozawa et al. (2009)	42,093 (≥40 years)	Green tea consumption (and other tea and coffee)	2006	Cross-sectional study set in Ohsaki Cohort 2006 study	Kessler 6-item psychological distress scale
Kuriyama et al. (2006)	1003 (≥70 years)	Green tea consumption (and other tea and coffee consumption)	2002	Cross sectional study of Comprehensive Geriatric Assessment (2002)	Questionnaire (comprehensive geriatric assessment), MMSE
Shimbo et al. (2005)	387 (20–69 years mean 46 years)	Green tea consumption (and other tea, coffee and caffeine-containing beverages consumption)	2002	Cross-sectional study	General health questionnaire, interview

EGCG, epigallocatechin gallate; UWIST, university of Wales of Science and Technology

MMSE, mini mental state examination.

were no *in vitro studies;* (4) Either green tea (green tea extract), EGCG, L-theanine or combinations of these were consumed (five studies were excluded; mainly because other compounds not naturally present in green tea were inextricably linked to the outcome); (5) There had to be an outcome related to brain functions, neurology or neuropsychology (fourteen results were excluded, as they produced a variety of different outcomes). This screening finally gave 21 results (Fig. 1). If only parts of a search result met all eligibility criteria, the parts that met the criteria were extracted and included—provided all five criteria were fulfilled.

Types of study design

Sixteen (16) of these 21 results were experimental trials and five were observational studies (Table 2). The experimental trials included four randomised controlled trials and twelve with repeated measures. The former investigating sub-acute or chronic effects of green tea or components thereof, the latter measuring acute green tea effects or acute effects of green tea components. The observational studies included one cohort study and four cross-sectional studies and measured for long-term green tea effects (Table 2).

Green tea and green tea extract (GTE)

Three experimental studies (Borgwardt et al., 2012; Park et al., 2011; Schmidt et al., 2014) investigated the effects of green tea or green tea extract: two the acute effects in healthy participants, one the chronic effects in patients with mild cognitive impairment (Park et al., 2011).

The neuroimaging study by Schmidt et al. (2014) employed functional magnetic resonance imaging (fMRI) to demonstrate that green tea acted on working memory by increasing connectivity from the right parietal lobule to the middle frontal gyrus and thus improved cognitive task performance in this way. Another neuro-imaging study by Borgwardt et al. (2012) was the first study to analyse green tea effects by means of fMRI and found that green tea significantly increased activation in the dorsolateral prefrontal cortex (DLPFC); the authors had suggested in advance that this was an "*a priori* region of interest", as it is important in processing working memory. The performance in the working memory task was not recorded. Thus, no cognitive benefit was demonstrated, as this study only measured brain activation. Park et al. (2011) showed that combined administration of GTE and L-theanine was beneficial to a more affected subgroup (Mini Mental State Examination (MMSE) 21–23) of their sample of participants suffering from mild cognitive impairment (MMSE 21–26), in that it increased verbal and visuospatial memory and attention. Twenty-three (23) random EEGs, equally divided between intervention and control, showed that this treatment significantly enhanced theta waves during the states "eyes open" and "reading" (but not in "eyes closed").

All of the five (Feng et al., 2010; Hozawa et al., 2009; Kuriyama et al., 2006; Shimbo et al., 2005; Tomata et al., 2012) observational studies investigated the long-term effects of exposure to green tea consumption. Tomata et al. (2012) showed that consumption of green tea reduced the risk of functional disability in a population of over sixty-five year olds; this was directly linked to the quantity habitually consumed. Feng et al. (2010) demonstrated that exposure enhanced performance in the MMSE, as well as the scores for memory, executive function and speed of information processing speed, all tested as part of a wide-range cognitive test battery in over 55-year olds. Hozawa et al. (2009) showed that green tea consumption reduced the odds ratio for physiological distress in a dose-dependent manner in a group of over 40-year olds. Kuriyama et al. (2006) substantiated considered that green tea consumption decreased the hazard ratio for cognitive impairment, which was defined as an MMSE score under 26.

Shimbo et al. (2005) studied a community based sample of 20- to 69-year olds, with a mean age of 46. They concluded that green tea had

Table 2
Cardiovascular, neuropsychological and imaging results of the reviewed studies.

Experimental studies
Healthy volunteers, acute green tea effects

	Cardiovascular effects	Neuropsychological effects	Neurocognitive effects	Brain functions
Schmidt et al. (2014)	Not tested	Not tested	Not significant; the magnitude of green tea induced increase in parieto-frontal connectivity positively correlated with improvement in task performance (p = 0.066)	Increased the working memory induced **modulation of connectivity** from the **right superior parietal lobule** to the **middle frontal gyrus.**
Borgwardt et al. (2012)	Not tested	Not tested	No data	Increased activation in dorsolateral prefrontal cortex bilaterally (p < 0.001*) (fMRI) *family wise-error adjusted
Scholey et al. (2012)	Not tested	Increased calmness (p = 0.04) and reduced stress	Increased calmness (p = 0.017) (VAS)	Increased overall alpha, beta and theta activity (LORETA: frontal gyrus and medial frontal gyrus, Brodmann area 6 and 10) (p = 0.001) in EEG (eyes open)
Wightman et al. (2012)	Not significant	Not significant	Not significant	135 mg EGCG reduced cerebral blood flow in the frontal cortex (p < 0.05) (NIRS, oxygenated haemoglobin)
Ota et al. (2014)	Not tested	Not tested	Not tested	Increases **sensorimotor gating** (percentage of prepulse inhibition) in dose range (200 mg and 400 mg, but not 600 mg) dosage independently (p < 0.05)
Yoto et al. (2012)	Reduced systolic blood pressure increment (p = 0.008) in high stress-responders	Reduced tension-anxiety scores (p = 0.004) (POMS)	Not significant	Not tested
Giesbrecht et al. (2010)	Combination: increased systolic blood pressure (p = <0.01)	Combination: increased self-reported alertness (p < 0.01) (VAS), reduced self-reported tiredness (p < 0.05) (task demand rating scale)	Combination: improved accuracy in attention-switching task (p < 0.01)	Not tested
Einöther et al. (2010)	Not tested	Not significant	Combination: improved accuracy in switch task (p = 0.003)	Not tested
Owen et al. (2008)	Not tested	Not significant	Combination: improved speed and accuracy in attention-switching task (p < 0.001), reduced susceptibility to distraction (p < 0.01)(word recognition)	Not tested
Kelly et al. (2008)	Not tested	Not tested	Combination: improved accuracy (p < 0.002) and hit rate (p < 0.016) in especially devised cognitive test	Combination: lowered overall tonic alpha amplitude (p < 0.02) (EEG)
Haskell et al. (2008)	Not tested	L-theanine: increased headache* (p < 0.05) combination: increased self-reported alertness(p < 0.01) (VAS), decreased self-reported tiredness*(p < 0.005), mental fatigue* (p < 0.05) and headache* (p < 0.05) (all VAS / CRVAS)	L-theanine: deteriorated serial sevens** (p < 0.05) combination: improved simple reaction time (p < 0.05), accuracy of RVIP (p < 0.001), numeric working memory reaction time (p < 0.05), delayed word recognition time (p < 0.05) and accuracy of sentence verification** (p < 0.05) ** data capture error: only 22 participants	not tested
Kimura et al. (2007)	Reduced heart rate increment (p < 0.05) and s-IgA increment (p < 0.01)	Reduced self-reported stress (p < 0.01) and self-reported anxiety (p < 0.01)(VAS and STAI)	Not tested	Not tested
De la Torre et al. (2014)	Increases plasma homocysteine levels (p = 0.024; biomarker for DYRK1A activity) after 1 month of treatment. Reduces plasma cholesterol (p = 0.02 and LDL cholesterol (p = 0.014) after 3 months of treatment.	Improved social functioning on the Kidscreen-27 quality of life index "social Support & Peers" (p = 0.05)	Increases visual memory recognition (p = 0.04)	Not tested
Park et al. (2011)	Not significant	Not tested	Increased both verbal/visuospatial memory (p = 0.0478)(Rey Kim memory test) and attention (p = 0.306, after 8 weeks) (Stroop colour-word	Increased theta waves during "eyes-open" (p < 0.005) and "reading" states (p < 0.05) (EEG of 23 random subjects)

EGCG, epigallocatechin gallate; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; LORETA, low resolution brain electromagnetic tomography; NIRS, near infrared spectroscopy; VAS, visual analogue scale.

CRVAS, caffeine research visual analogue scale; EEG, electroencephalography; VAS, visual analogue scale RVIP, rapid visual information processing; s-IgA, secretory immunoglobulin A; STAI, state-trait anxiety inventory.

Table 2 (continued)

Experimental studies
Healthy volunteers, acute green tea effects

	Cardiovascular effects	Neuropsychological effects	Neurocognitive effects	Brain functions
Ritsner et al. (2011)	Not tested	Reduced positive ($p = 0.004*$) and activation factor ($p = 0.006*$) (in 5-dimensional PANSS), positive ($p = 0.009**$) and general psychopathology sub-scales ($p < 0.001**$) (in 3-dimensional PANSS) and anxiety scores ($p = 0.015**$) (HARS) *Bonferroni correction for 3 tests was applied **Bonferroni correction for 5 tests was applied	Not significant	reading test) in more affected subgroup (MMSE-K 21–23) Not tested
Brown et al. (2009)	Reduced diastolic blood pressure ($p = 0.014$)	Increased hedonic tone ($p = 0.048$)	Not tested	Not tested

DYRK1A, dual specificity tyrosine-(Y)-phosphorylation-regulated kinase 1A; EEG, electroencephalography; HARS, Hamilton anxiety rating scale; LDL, low-density lipoprotein; MMSE-K, mini mental state examination—Korean; PANSS, positive and negative syndrome scale.

Observational studies
Long-term green tea effects

	Cardiovascular effects	Neuropsychological effects	Neurocognitive effects	Brain functions
Tomata et al. (2012)	Tested, yet no supplied data	Not tested, see Hozawa et al.	Decreased OR for functional disability related to dosage: 1–2 cups/d OR 0.9, 3–4 cups/d OR 0.76 and $\geq$5 cups/d OR 0.67 in reference to < 1 cups/d ($p < 0.001$)	Not tested
Feng et al. (2010)	Tested, yet mixed with other tea and coffee consumption	Tested, yet mixed with other tea and coffee consumption	Increased performance in MMSE ($p = 0.02$), memory-score ($p = 0.01$), executive function-score ($p = 0.01$) and information processing speed-score ($p = 0.04$)	Not tested
Hozawa et al. (2009)	Associated with less history of stroke ($p < 0.001$) and more history of cancer ($p < 0.007$)	Reduced OR for physiological distress (Kessler 6-item physiological distress scale) related to dosage: 1–2 cups/d OR 0.95, 3–4 cups/d OR 0.89, >5 cups/d OR 0.80 in reference to <1 cups/d ($p < 0.001$)	Not tested, see Tomata et al. [46]	Not tested
Kuriyama et al. (2006)	Not significant	Not significant	Decreased the OR of cognitive impairment (MMSE < 6): 0.57–0.86 cups/d OR 0.62, 2–3 cups/d OR 0.42, $\geq$ 4 cups/d OR 0.49 ($p < 0.004$) in reference to $\leq$0.43 cups/d ($p = 0.004$)	Not tested
Shimbo et al. (2005)	Not tested	Not significant	Green tea effects not significant, daily caffeine (including green tea) intake of 100 mg increased risk for mental ill-health among females, OR1.26 ($p = 0.04$)	Not tested

1 cup of tea equals 100 ml; MMSE, mini mental state examination; OR, odds ratio.

no significant neuropsychological or cognitive effects.

Epigallocatechin gallate (EGCG)

Four experimental studies (Brown et al., 2009; De la Torre et al., 2014; Scholey et al., 2012; Wightman et al., 2012) analysed the effects of EGCG. Two of these used did so analysing acute effects in healthy volunteers. One study was restricted to obese patients (Brown et al., 2009) and one to patients with Down's syndrome (De la Torre et al., 2014) and examined long-term effects.

Scholey et al. (2012) reported that EGCG-intake had a significant calming effect and relieved stress and increased the overall activity of alpha-, beta- and theta-waves in the EEG. A low resolution brain electromagnetic tomogram (LORETA) showed that the frontal and medial frontal gyrus were the source of this activation. With near infrared spectroscopy (NIRS), Wightman et al. (2012) showed that the administration of EGCG reduced cerebral blood flow in the frontal cortex. De la Torre et al. (2014) investigated the effects of EGCG in patients with Down's syndrome and found that treatment significantly improved visual memory recognition after one month, and social functioning and increased plasma homocysteine levels (hcy). It was shown with transgenic mice that hcy is a valid biomarker for hippocampal *dual specificity tyrosine-(Y)-phosphorylation-regulated kinase 1A* (Dyrk1A) activity. Therefore, the increased hcy levels were interpreted as EGCG-mediated inactivation of Dyrk1A—a kinase which when over-expressed may be responsible for some of the neurocognitive deficits in Down's syndrome. Brown et al. (2009) demonstrated the ability of EGCG to reduce diastolic blood pressure and to improve the hedonic tone. These results were a secondary outcome of an investigation of potential insulin-modifying properties of EGCG in obese patients.

ʟ-Theanine

Ten experimental studies (Einöther et al., 2010; Giesbrecht et al., 2010; Haskell et al., 2008; Kelly et al., 2008; Kimura et al., 2007; Ota et al., 2014; Owen et al., 2008; Park et al., 2011; Ritsner et al., 2011; Yoto et al., 2012) focussed on the effects of ʟ-theanine intake. Nine (Einöther et al., 2010; Giesbrecht et al., 2010; Haskell et al., 2008; Kelly et al., 2008; Kimura et al., 2007; Ota et al., 2014; Owen et al., 2008; Park et al., 2011; Yoto et al., 2012) of these employed within-subject designs and healthy participants for acute effects, whereas one randomised controlled trial investigated these long-term effects in a population of patients with the diagnosis of schizophrenia or a schizoaffective disorder (Ritsner et al., 2011)'. Three studies (Kimura et al., 2007; Ota et al., 2014; Ritsner et al., 2011) investigated the isolated effects of ʟ-theanine; one explored the effect of ʟ-theanine combined with GTE (Park et al., 2011) (and was already summarised in the previous chapter), while the other six (Einöther et al., 2010; Giesbrecht et al., 2010; Haskell et al., 2008; Kelly et al., 2008; Owen et al., 2008; Yoto et al., 2012) included caffeine, as ʟ-theanine naturally occurs together with caffeine. Of these studies, only the outcomes for ʟ-theanine alone or for ʟ-theanine and caffeine together were extracted (and identified accordingly)—the outcome caused by caffeine alone was not extracted.

Ota et al. (2014) demonstrated that ʟ-theanine increased prepulse inhibition (PPI) and thus sensorimotor gating. The increase in PPI was not correlated with the dose of ʟ-theanine. Yoto et al. (2012) discovered that ʟ-theanine reduced the elevation of systolic blood pressure caused by a stressor-task in a subgroup they defined as "high stress-responders"; these were participants whose blood pressure was elevated by at least 9 mmHg during the stress task under placebo treatment. Moreover, this intervention reduced tension and anxiety (by decreasing tension-anxiety scores in the profile of mood states). Giesbrecht et al. (2010) reported that combined treatment of ʟ-theanine and caffeine not only raised systolic blood pressure, but also made the volunteers feel more alert and less tired. Moreover, it enhanced attention (measured by an attention-switching task). On the other hand, Einöther et al.

(2010)—using a very similar study setup—merely produced evidence for the attention-improving properties of combined treatment using an attention switching task. However, there was no increase in self-reported alertness, contrasting Giesbrecht et al. (2010) findings. Owen et al. (2008) also showed that a combination of ʟ-theanine and caffeine led to a shorter response time and greater accuracy in an attention-switching task. Kelly et al. (2008) found that ʟ-theanine only had a beneficial effect on accuracy and hit rate in a "behavioural test" (relative to a placebo condition and a no-intervention condition) when combined with caffeine, but not on its own. The same was true of the diminution of the overall tonic alpha amplitude in EEG. Haskell et al. (2008) reported that intake of ʟ-theanine alone led to headache and worsened the performance in a test with seven serial subtractions, whereas the combination of ʟ-theanine and caffeine made the participants feel more alert, less tired and less afflicted with mental fatigue and headache, as shown by a visual analogue scale. In addition, this treatment was favourable for simple reaction time, the reaction time in testing numerical working memory, accuracy in rapid visual information processing, and accuracy of sentence verification, as well as improving scores in delayed word recognition time. Kimura et al. (2007) found that ʟ-theanine reduced stress-induced heart rate and increases in secretory immunoglobulin A. They also reported a reduction in perceived stress and anxiety, using visual analogue scales and a state-trait anxiety inventory.

Ritsner et al. (2011) proved demonstrated that augmentation of antipsychotic medication with ʟ-theanine was beneficial to his group of patients suffering from schizophrenia or schizoaffective disorder. The positive and negative syndrome scale (PANSS) revealed a reduction in positive and general psychopathology in its three dimension model. The amelioration of negative syndromes was not significant after Bonferroni correction. PANSS also revealed a reduction in activation factor and positive factor in its five-dimensional model. Moreover, Ritsner et al. (2011) found that the treatment lowered anxiety according to the Hamilton anxiety rating scale.

Acute cognitive effects

Five experimental cross-over studies (Giesbrecht et al., 2010; Einöther et al., 2010; Owen et al., 2008; Kelly et al., 2008; Haskell et al., 2008) on healthy participants focussed on the acute cognitive effects of ʟ-theanine combined with caffeine.

Giesbrecht et al. (2010) reported that combined treatment of ʟ-theanine and caffeine not only raised systolic blood pressure, but also enhanced attention (measured by an attention-switching task). Einöther et al. (2010) produced evidence for the attention-improving properties of combined treatment using an attention switching task. Owen et al. (2008) also showed that a combination of ʟ-theanine and caffeine led to a shorter response time and greater accuracy in an attention-switching task. Kelly et al. (2008) found that ʟ-theanine only had a beneficial effect on accuracy and hit rate in a "behavioural test" (relative to a placebo condition and a no-intervention condition) when combined with caffeine, but not on its own. Haskell et al. (2008) reported that intake of ʟ-theanine alone led to headache and worsened the performance in a test with seven serial subtractions, whereas the combination of ʟ-theanine and caffeine was favourable for simple reaction time, the reaction time in testing numerical working memory, accuracy in rapid visual information processing, and accuracy of sentence verification, as well as improving scores in delayed word recognition time.

Acute mood effects

Five experimental cross-over studies (Scholey et al., 2012 Yoto et al., 2012; Kimura et al., 2007 Giesbrecht et al., 2010; Haskell et al., 2008) with healthy participants investigated acute effects on mood: one of EGCG (Scholey et al., 2012), two of ʟ-theanine(Yoto et al., 2012; Kimura et al., 2007) and two of ʟ-theanine combined with caffeine

(Giesbrecht et al., 2010; Haskell et al., 2008).

Scholey et al. (2012) reported that EGCG-intake had a significant calming effect and relieved stress as shown by visual analogue scales. Yoto et al. (2012) discovered that L-theanine reduced the elevation of systolic blood pressure caused by a stressor-task in a subgroup they defined as "high stress-responders"; these were participants whose blood pressure was elevated by at least 9 mmHg during the stress task under placebo treatment. Moreover, this intervention reduced tension and anxiety (by decreasing tension-anxiety scores in the profile of mood states). Kimura et al. (2007) found that L-theanine reduced stress-induced heart rate and increases in secretory immunoglobulin A. They also reported a reduction in perceived stress and anxiety, using visual analogue scales and a state-trait anxiety inventory. Giesbrecht et al. (2010) reported that combined treatment of L-theanine and caffeine made the volunteers feel more alert and less tired. On the other hand, Einöther et al. (2010)—using a very similar study setup—found no increase in self-reported alertness, contrasting Giesbrecht et al. (2010) findings. Haskell et al. (2008) reported that intake of the combination of L-theanine and caffeine made the participants feel more alert, less tired and less afflicted with mental fatigue and headache, as shown by a visual analogue scale.

Chronic effects (associated with habitual consumption)

Four randomised controlled trials (Park et al., 2011; De la Torre et al., 2014; Brown et al., 2009; Ritsner et al., 2011) on different kinds of clinical groups investigated non-acute effects of green tea or green tea components. Two did so on cognitive effects, one with GTE combined with L-theanine (Park et al., 2011) and one with EGCG (De la Torre et al., 2014). Two more trials focussed on effects on mood, one of EGCG (Brown et al., 2009) and one of L-theanine (Ritsner et al., 2011). Furthermore, four observational studies investigated long-term cognitive effects (Feng et al., 2010; Kuriyama et al., 2006; Shimbo et al., 2005; Tomata et al., 2012) and one long-term effects on mood (Hozawa et al., 2009) of habitual green tea consumption on samples of the general population.

Park et al. (2011) showed that combined administration of GTE and L-theanine—twice daily over 16 weeks—was beneficial to a more affected subgroup (Mini Mental State Examination (MMSE) 21-23) of their sample of participants suffering from mild cognitive impairment (MMSE 21–26), in that it increased verbal and visuospatial memory and attention. De la Torre et al. (2014) investigated the effects of daily EGCG administration over twelve weeks in patients with Down's syndrome and found that treatment significantly improved visual memory recognition after one month, and social functioning and increased plasma homocysteine levels (hcy). It was shown with transgenic mice that hcy is a valid biomarker for hippocampal *dual specificity tyrosine-(Y)-phosphorylation-regulated kinase 1A* (Dyrk1A) activity. Therefore, the increased hcy levels were interpreted as EGCG-mediated inactivation of Dyrk1A—a kinase which when over-expressed may be responsible for some of the neurocognitive deficits in Down's syndrome. Brown et al. (2009) demonstrated the ability of EGCG to reduce diastolic blood pressure and to improve the hedonic tone. These results were a secondary outcome of an investigation of potential insulin-modifying properties of EGCG in obese patients over eight weeks. Ritsner et al. (2011) ~~proved~~ demonstrated that augmentation of anti-psychotic medication with L-theanine over eight weeks was beneficial to his group of patients suffering from schizophrenia or schizoaffective disorder. The positive and negative syndrome scale (PANSS) revealed a reduction in positive and general psychopathology in its three dimension model. The amelioration of negative syndromes was not significant after Bonferroni correction. PANSS also revealed a reduction in activation factor and positive factor in its five-dimensional model. Moreover, Ritsner et al. (2011) found that the treatment lowered anxiety according to the Hamilton anxiety rating scale.

Tomata et al. (2012) showed that consumption of green tea reduced the risk of functional disability in a population of over sixty-five year olds; this was directly linked to the quantity habitually consumed. Feng et al. (2010) demonstrated that exposure enhanced performance in the MMSE, as well as the scores for memory, executive function and speed of information processing speed, all tested as part of a wide-range cognitive test battery in over 55-year olds. Kuriyama et al. (2006) substantiated ~~considered~~ that green tea consumption decreased the hazard ratio for cognitive impairment, which was defined as an MMSE score under 26.

Shimbo et al. (2005) studied a community based sample of 20- to 69-year olds, with a mean age of 46. They concluded that green tea had no significant neuropsychological or cognitive effects. Hozawa et al. (2009) showed that green tea consumption reduced the odds ratio for physiological distress in a dose-dependent manner in a group of over 40-year olds.

Effects on brain function

Six experimental cross-over studies (Borgwardt et al., 2012; Schmidt et al., 2014; Scholey et al., 2012; Wightman et al., 2012; Ota et al., 2014; Kelly et al., 2008) on healthy participants produced results on brain function: two with GTE (Borgwardt et al., 2012; Schmidt et al., 2014) two with EGCG (Scholey et al., 2012; Wightman et al., 2012), one with just L-theanine(Ota et al., 2014) and one with L-theanine combined with caffeine (Kelly et al., 2008). Also, one randomised controlled trial (Park et al., 2011) researching the effects of a combination of GTE and L-theanine contained results pertaining to brain functions.

The neuroimaging study by Schmidt et al. (2014) employed functional magnetic resonance imaging (fMRI) to demonstrate that green tea in the form of GTE acted on working memory by increasing connectivity from the right parietal lobule to the middle frontal gyrus and thus improved cognitive task performance. Another neuro-imaging study by Borgwardt et al. (2012) was the first study to analyse green tea effects by means of fMRI and found that GTE significantly increased activation in the dorsolateral prefrontal cortex (DLPFC); the authors had suggested in advance that this was an "*a priori* region of interest", as it is important in processing working memory. Scholey et al. (2012) reported that EGCG-intake increased the overall activity of alpha-, beta- and theta-waves in the EEG. A low resolution brain electromagnetic tomogram (LORETA) showed that the frontal and medial frontal gyrus were the source of this activation. With near infrared spectroscopy (NIRS), Wightman et al. (2012) showed that the administration of EGCG reduced cerebral blood flow in the frontal cortex. Ota et al. (2014) demonstrated that L-theanine increased prepulse inhibition (PPI) and thus sensorimotor gating. The increase in PPI was not correlated with the dose of L-theanine. Kelly et al. (2008) found that L-theanine only diminished the overall tonic alpha amplitude in EEG when combined with caffeine, but not on its own.

Park et al. (2011) administered a combination of GTE and L-theanine twice daily over 16 weeks and performed 23 random EEG on their sample of participants suffering from mild cognitive impairment (MMSE 21–26), equally divided between intervention and control. The intervention significantly enhanced theta waves during the states "eyes open" and "reading" (but not in "eyes closed").

Quality assessment

Our assessment of the sixteen experimental studies was in accordance with the Final Delphi List (on study level, *e.g.* risk of bias) and showed that the general quality was good (8.25/9). The studies of Scholey et al. (2012), Giesbrecht et al. (2010), Einöther et al. (2010), Owen et al. (2008), Haskell et al. (2008), Ritsner et al. (2011) and Park et al. (2011) were excellent (9/9), whereas the paper of Kelly et al. (2008) scored the lowest and was still deemed fair (6/9). This assessment took place at the study level.

Our assessment of the five observational studies was performed with the Newcastle–Ottawa quality assessment scale (on the study and outcome level, *e.g.* risk of bias) and showed that the average quality was good (6.7/9). Tomata et al. (2012) cohort study was at the high end of good (8/9). This assessment took place at the study level and at the outcome level (*the entire quality assessment can be found in Appendix II*).

Discussion

This systematic review aimed to establish the current status of knowledge regarding the effects of green tea consumption on cognition and human brain function. Green tea and its main ingredients, EGCG and L-theanine, can enhance cognition, neuropsychology and brain functions, as the majority of the reviewed studies suggest. The research findings on habitual, daily green tea consumption of at least 100 ml per day suggest that the principle long-term benefits are improved mental facilities, a more relaxed state of mind and a lower risk of dementia. Those effects appear to increase dose-dependently up to a consumption of 500 ml per day—an even greater consumption of green tea was not investigated. No author reported disparate findings. Most of the authors attribute the beneficial effects of green tea to the high levels of EGCG and other antioxidants in green tea leaves (Higdon and Frei, 2003; Nagle et al., 2006; Scapagnini et al., 2011) and iron-chelation (Mandel et al., 2011). L-theanine and vitamin C are both present in the beverage and may have secondary long-term beneficial effects. It seems unlikely that vitamin is the sole cause of the discovered benefits, as Kuriyama et al. (2006) adjusted for non-dietary vitamin C intake and found little change in their results.

The studies investigating the controlled administration of green tea extract found short-term benefits in memory and attention as well as an increase in the activation of a brain area responsible for mediating working memory, as demonstrated by fMRI. These effects may be linked to the antioxidant (Higdon and Frei, 2003; Nagle et al., 2006; Scapagnini et al., 2011) and iron-chelating (Davinelli et al., 2012; Levites et al., 2002; Mandel et al., 2011) qualities of EGCG present in the extract. EGCG may also protect against β-amyloid neurotoxicity, perhaps through the protein kinase C pathway, as found in a study in mice (Levites et al., 2003). On the other hand, Schmidt et al. (2014) proposed that green tea extract might enhance parieto-frontal connectivity by modulating the synaptic plasticity of NMDA-receptors. This effect is modulated by working memory and is measurable using fMRI methods.

Administration of EGCG alone was found to have a calming effect on mood as well as an impact on brain functions, as detected by EEG and NIRS. There was an overall increase in alpha, beta and theta activity which could be linked to areas in the frontal gyrus; this is consistent with the increased activity of the working memory indicated in fMRI, since the scrutinised functional structure, which is the dorsolateral prefrontal cortex, is mostly located in the anatomical region of the frontal gyrus. However, the NIRS results suggest reduced cerebral blood flow in the frontal cortex and a lower concentration of both oxygenated and total haemoglobin after administration of the lower of two trial doses of EGCG. The calming EGCG effect may be linked to interaction with the $GABA_A$ receptor (Adachi et al., 2006). The only documented cognitive improvement of EGCG-only therapy was reported in patients with Down's syndrome, where EGCG normalised hippocampal Dyrk1A activity (De la Torre et al., 2014). Improvements in object recognition were attributed to EGCG effects in the hippocampus and perirhinal cortex; benefits in working memory indicate effects in the prefrontal cortex.

Few short-term beneficial effects were reported with L-theanine alone: two studies found reductions in stress and tension. A third study (Feng et al., 2010) failed to confirm the relaxing qualities of L-theanine, but found that it caused headaches and decreased cognitive performance in the task of subtracting serial sevens, the latter being consistent with previous findings of detrimental L-theanine effects in an

auditory attention task (Gomez-Ramirez et al., 2007). In contrast, L-theanine was shown to increase prepulse inhibition to auditory stimuli, resulting in fewer startling responses and possibly increased focus (Ota et al., 2014). The study that supplemented L-theanine to patients diagnosed with schizophrenia and receiving antipsychotic drugs also failed to identify cognitive improvements, but also documented a desirable long-term effect on mood (Ritsner et al., 2011). Kakuda's review (Kakuda, 2011) of animal model studies on the neuroprotective effects of L-theanine described several mechanisms by which the glutamate analogue L-theanine might protect neuronal function. The glutamate excitotoxicity of extracellular glutamate may be reduced by antagonistic action on the glutamate receptors NMDA, AMPA and kainate, or by acting on the glutamine transporter.

Beneficial short-term effects were documented for a combination of L-theanine and caffeine in every study in which this was tested. These generally differed from the effects of L-theanine or caffeine alone, which perhaps indicate that the two substances act synergistically, although this has not yet been investigated at the receptor level (Haskell et al., 2008). Even though no acute cognitive effects of L-theanine, but many such effects of caffeine are reported in the scrutinised studies, the documented cognitive effects of a combination of the two compounds cannot be attributed to caffeine alone: Haskell et al. (2008) found that memory was unaffected by both caffeine or L-theanine, whereas the combined substances significantly improved memory measures. Similarly, Kelly et al. (2008) recorded no effect of either L-theanine or caffeine on hit-rate, yet a significant improvement when the two interventions were combined. This L-theanine potentiation of acute cognitive effects of caffeine perhaps indicates that the two substances act synergistically, although this has not yet been investigated at the receptor level (Haskell et al., 2008). The spectrum of the recorded acute effects of L-theanine combined with caffeine is broad—ranging from reducing mental tiredness to improving cognitive qualities related to attention and memory, to reduced overall tonic alpha amplitude in the EEG. No documented effect of the combined substances is detrimental. While the interpretation of the EEG findings (Kelly et al., 2008) is difficult to put into context, the effects cannot be regarded as detrimental, as cognitive performance was improved in speed and accuracy. It is unclear whether L-theanine increases (Nobre et al., 2008) or reduces (Kelly et al., 2008) alpha activity in the EEG and how the provoked changes in alpha activity should be interpreted; either could be beneficial (Kelly et al., 2008), *e.g.* through a shift from background alpha activity towards attention-related alpha activity during demanding tasks (Gomez-Ramirez et al., 2007).

A review by Bryan focussed on neuropsychological effects and analysed studies on caffeine and L-theanine. This concluded that the combined substances have more effect on cognitive tasks than on mood (Bryan, 2008). Another review by Camfield et al. (2014) contains a meta-analysis of L-theanine and caffeine studies and concluded that a combination of these two compounds increased both self-reported alertness as well as switching task accuracy in the first two hours after consumption.

There is a doubtlessly a certain degree of overlap between green tea effects research and caffeine effects research. Even though the latter is not a focus of the systematic review, it is interesting to note, that apart from the well documented acute cognitive effects of caffeine in healthy humans, there is evidence that is suggestive of long term memory consolidation (Borota et al., 2014).

When comparing green tea (compounds) with nicotine, it is noticeable that nicotine has been shown to act on (among other loci) on the DLPFC as seen in fMRI (Ettinger et al, 2009)—reminiscent of GTE. Ettinger et al. found that nicotine acutely improved oculomotor performance (anti-saccade latencies) in both healthy non-smokers and otherwise healthy smokers. Moreover, parallel to Ritsner et al. (2011) findings of L-theanine benefits for patients suffering from schizophrenia or schizoaffective disorder Kumari et al. (2005) argue that nicotine entails cognitive benefits for patients affected with schizophrenia. In an

effort to gauge the different self-medication hypotheses explaining the wide-spread tobacco use among schizophrenics, Kumari et al.—among other mechanisms—discuss the nicotine effect of increased PPI to startle response on auditory stimuli. Thus, nicotine appears to act in a similar way as L-theanine in the trial of Ota et al. (2014). A review researching the supplementation of the amino-acid tyrosine (Jongkees et al., 2015)—the precursor to dopamine and norepinephrine—in both healthy volunteers and clinical groups concluded, that tyrosine administration could indeed improve cognitive function in both groups. However, the proposed mode of action mainly seems to come to fruition by furnishing the "fuel" once neurotransmitter supply is depleted (*e.g.* during multi-tasking or during demanding single-tasks). This proposed principle of action is fundamentally different from the postulated green tea effects, even though the cognitive benefits of tyrosine administration or green tea supplementation could in instances appear similar. Another psychoactive substance worth comparing to green tea is methylphenidate—*e.g.* through the study on healthy volunteers, with two cognitive tasks (motor response inhibition) and fMRI results of Costa et al. (2013). Similar to green tea, methylphenidate impacted mood, cognition and produced discernible fMRI peaks. There are however important differences: the changes on mood were broader (every dimension of VAS was increased except for „tired"), the reported cognitive benefits were in the domain of motority and the observed fMRI-activation resulted in the putamen. D-amphetamine is another known psychoactive substance to affect both mood and cognitive function—as illustrated in a trial on healthy subjects investigating oculomotor performance and impact on mood (Allman et al., 2010). Allman et al. found that D-amphetamine reduced anti-saccade errors, had a significant yet difficult to interpret influence on anti-saccade latency and significantly impacted mood in POMS (five out of six dimensions) and most notably led to elation.

This systematic review has several limitations. Firstly, no quantitative meta-analysis could be performed due to the heterogeneity of the retrieved data. One aspect of the mentioned heterogeneity is the presence of both healthy volunteers and different kinds of patients in the body of the reviewed data. Even though the studies included might cover a broad range of subjects, from patients to non-patients, the results show that green tea administration can lead to beneficial changes also in a pathological population. Moreover, we were very careful in the manuscript to use caution from generalizing the reported results of clinical studies.

Secondly, the necessary simplifying assumption that green tea effects are the effects of two components that can be found almost exclusively in green tea does not account for the possible effects or interactions of other components of *Camellia sinensis*. Also, the precise dose threshold for both EGCG and L-theanine for reliable acute effects on either cognition or mood could not be established neither in the reviewed body of work nor in the general scientific literature. The observed approach to determine a relevant intervention was either to broadly scatter the dosages of the compound in question (Ota et al., 2014; L-theanine 200 mg, 400 mg and 600 mg) or—in all other cases—start from dosages that would typically be found in one unit of consumption (*e.g.* one cup of green tea) and then increase the studied substance up to tenfold. Similarly, the minimal period of time over which the long-term effective 100 ml of green tea should be consumed so as to confidently expect cognitive and neuropsychological benefits could not be determined.

Thirdly, although data was extracted following PICOS (patient-intervention-control-outcome-study design) and main study characteristics, no validated tool for data extraction was used and there was only one reviewer.

Another difficulty arose in the lack of an evidence-based quality assessment tool for cross-sectional studies. What is more important, even though DELPHI and Newcastle–Ottawa-Scale assess the most common biases, the problem of publication bias remains unaccounted for.

Conclusions

While this systematic review found a reasonable amount of evidence that both EGCG and L-theanine exhibit neuroprotective activity and that L-theanine (and to a lesser degree of EGCG) influence mood, the extracted data suggests that the various improvements in cognitive faculties linked to green tea consumption are not the consequence of a single component. The improvements in cognitive tasks in the reviewed studies are strongly linked to the presence of both caffeine and L-theanine. Further research is needed to establish the minimal dosage of green tea or green tea components to reliably elicit either acute or chronic effects, as well as what minimal period of time will result in long-term green tea effects. Another question for further research to investigate is the interaction of the two compounds and to establish whether EGCG too would further enhance cognitive performance in combination with caffeine. Also, more research is needed to corroborate the claim of EGCG effects on mood. Given the success of L-theanine supplementation of antipsychotic treatment for schizophrenia or schizoaffective disorder, further research is needed to identify other psychiatric treatments that could benefit from the anxiolytic properties and reduction in positive symptoms from L-theanine. The extracted data suggests that it would be desirable for more Westerners to change their lifestyle to include habitual, daily consumption of green tea of at least 100 ml per day, in order to protect their neurocognitive function.

Conflict of interest

There is no conflict of interest. There was no funding involved in the development of this review.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.phymed.2017.07.008.

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