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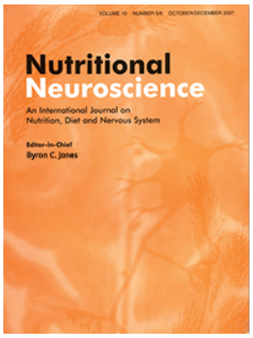

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Acute effects of combined Bacopa, American ginseng and whole coffee fruit on working memory and cerebral haemodynamic response of the prefrontal cortex: a double-blind, placebo-controlled study

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ABSTRACT

Objective: This study assessed whether a multi-ingredient herbal supplement containing *Bacopa monniera* (BM), *Panax quinquefolius ginseng* (PQ) and whole coffee fruit extract (WCFE) could enhance cognitive performance and cerebral-cortical activation during tasks of working memory and attention.

Method: In a randomised, double-blind, placebo-controlled, between-group study, 40 healthy adults between 18–60 years ($M = 34.46$ SD = 12.95) completed tasks of working memory and attention at baseline and 45 min post active or placebo supplement consumption. During the cognitive testing, changes in hemodynamic response in the prefrontal cortex (PFC) were continuously measured using functional near-infrared spectroscopy (fNIRS).

Results: Working memory task performance on the N-back task was significantly improved following active supplement consumption compared to placebo in terms of accuracy ($p < .01$) and response time ($p < .05$). Improved performance was associated with a reduction of PFC activation ($p < .001$) related to effortful mental demand, reflecting increased neural efficiency concomitant with improved cognitive performance. The effects were independent of background demographics variables and changes in blood glucose response and mood.

Discussion: This is the first report of acute effects on cognitive performance in healthy adults following intake of a combined, multi-ingredient herbal supplement with concomitant changes in cerebral haemodynamic response. The potential synergistic effects of polyphenolic compounds on neurocognitive function and fNIRS use in nutritional intervention studies, poses a significant increase in the capacity to understand the effects of dietary compounds on the brain.

KEYWORDS
Nutrition; cognition; polyphenols; working memory; mood; herbal extracts; fNIRS; intervention

Introduction

There has been a rapid increase in interest regarding the role of herbs and nutraceuticals in enhancing neurocognitive function in healthy adults. Recently, considerable attention has been given to individual high-quality plant extracts such as ginseng, Bacopa and *Ginko biloba* and their potential neurocognitive benefits [1]. Whilst the biological mechanisms of effect through which herbs and nutraceuticals influence neurocognitive functioning are poorly understood, emerging evidence indicates that individual bioactive chemicals and phytochemicals from food and standardised extracts play an important role in physical and neurological health [2]. Broadly, as a group, polyphenolic compounds have gained considerable attention for their potential role in preserving and maintaining cognitive function and preventing neurodegenerative disorders [3].

Herbal extracts contain many active components, which in synergy may influence multiple metabolic, hormonal and neuronal systems that affect behavioural patterns and responses. In isolation, experimental and longitudinal studies have identified numerous biological effects of active polyphenolic compounds such as glucoregulation, anti-inflammatory and antioxidant effects as well as neuronal preservation, neurogenesis, and increasing cerebral blood flow [4]. Improvements in these biological mechanisms are associated with a lower risk of cognitive disorders and cognitive impairments, and some small improvements in cognitive task performance. For example, high dietary polyphenol intake is associated with reduced risk of dementia [5], and intervention studies have shown beneficial, cognitive-enhancing effects of polyphenol-rich foods such as tea, coffee, berries, wine and cocoa in young and older adults [6]. However, elucidating the potential interactions between

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active components and the complex polypharmacological properties of dietary and herbal extracted compounds results in several challenges; including understanding the dose- and time-dependent effects on biological systems, which remain mostly unknown.

There is growing evidence that herbal extracts, such as *Bacopa monniera* (BM) and *Panax quinquefolius ginseng* (PQ: American ginseng) acutely enhance cognitive performance. Specifically, an acute study of BM showed change from baseline improvement on Stroop performance (a measure of attention) at 1 and 2 h post 640 mg dose of BM, and at 1 h post 320 mg BM dose compared to placebo in healthy adults [7]. However, no acute cognitive change was detected following 300 mg of BM, 2 h post dose [8]. The unknown pharmacodynamic effects of Bacopa absorption, and the role of active saponins (a form of polyphenol) Bacoside A, and Bacoside B in the central nervous system are areas for further research. In particular, complex dose x time effects of BM in cognitive challenging paradigms, following acute and chronic intake are still to be characterised. In contrast, administering American ginseng has been shown to improve working memory (WM) performance, with WM tasks differentially improved by a 200 mg dose (with time- and task-specific benefits associated with various doses) during acute testing. Also, tasks of attention have been shown to be significantly improved by 100 mg at 1, 2, 3 and 6 h post dose, and by 200 and 400 mg after 6 h [9].

Polyphenol-rich, caffeine-containing extracts, such as whole coffee fruit extract (WCFE), are also potential candidates for maintaining biological systems that underpin neurocognitive function [10]. Recent research has shown that an acute 100 mg WCFE dose in healthy adults significantly increases measures of Brain-derived neurotrophic factor (BDNF), which is a neurotrophin that is important for learning and memory processes. However, much less is known about how these compounds (i.e. BM, ginseng and polyphenol-rich chlorogenic acid and caffeine-containing extracts), can affect cognitive change in concert. The challenge to current research in this field is to understand how these compounds may produce synergistic effects and if specific quantities of extracts are needed for these effects to occur, if indeed improved cognitive outcomes can be demonstrated.

Gold-standard neuroimaging modalities such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) have traditionally been used to elucidate the neural mechanisms of action underpinning these extracts. More recently, the use of the optical imaging technique functional near-infrared spectroscopy (fNIRS), has gained increasing utility in understanding the role of nutrition and dietary supplements on brain function [11]. FNIRS is a relatively new neuroimaging method that uses NIR light to measure the cerebral haemodynamic response (i.e. exchange between oxy- and deoxy-haemoglobin [O_2Hb and HHb]) in localised brain regions. The advantages of fNIRS over other neuroimaging modalities are its increased portability, comparatively low cost and high reliability to fMRI measures during cognitively demanding tasks [12].

Using fNIRS, several acute studies have demonstrated changes in cerebral blood volume and haemodynamic responses following the administration of caffeine and polyphenols. Higashi et al. [13] found reductions in cerebral blood volume in the prefrontal cortex (PFC) at rest following 180 mg of pharmacopoeia caffeine administration compared to no treatment. However, the authors reported no differences in haemodynamic responses to cognitive tasks between the caffeine and no-caffeine groups, despite cognitive performance improvements following caffeine administration. In a subsequent study, Kennedy and Haskell [14] reported a decrease in total O_2Hb of the PFC during task performance following a 75 mg dose of caffeine. The authors then investigated the effects of polyphenols and demonstrated a dose-dependent increase in total O_2Hb and HHb following 250 and 500 mg of resveratrol respectively following 45 min absorption time [15], and a decrease in total O_2Hb following a 135 mg dose of epigallocatechin gallate during cognitive tasks [16]. However, there was no effect on cognitive task performance in either study.

Given that existing research indicates extracts have a neurocognitive effect in isolation, this study instead aimed to provide a preliminary, pilot assessment of whether the combination of standardised extracts BM, PQ and WCFE, could enhance cognitive performance (working memory and attention tasks). In addition, the impact of the combined extracts on cerebral activation of the PFC was assessed via fNIRS during task performance.

Method

Participants

A total of 40 healthy adults (21 female, 19 male) aged 18–60 years ($M = 34.46$, $SD = 12.95$) participated in the study. Prior to testing, participants provided written consent and completed a background health and demographic questionnaire to determine the following: age, height and weight (to calculate body mass index [BMI]), years of education, hours worked per week, self-rated health (scale from 1 = poor to 5 = excellent), the number of dietary supplements and medications used, total hours spent exercising per week, and alcohol

consumption (number of standard drinks consumed in a typical week). Descriptive statistics for the two supplement groups are presented in Table 1.

Participants were recruited via an online flyer through social media outlets and word of mouth. Interested parties contacted the researchers by phone or E-mail. Participants were provided with a $50 gift card upon completing the appointment to reimburse travel and parking costs at the University. The study was granted ethics approval by the Human Research Ethics Committee of Central Queensland University (HREC: 0000021386). Participants were eligible to participate if they self-reported they were in good health and reported, at most, low dose, stable, preventive health medication use (e.g. hormone replacement therapy or consistent medication use for blood pressure, cholesterol, or thyroid), no history of head injury, stroke or neurological condition, heart disease, diabetes, or gastrointestinal conditions that may impact food metabolism. Participants were also excluded at the time of testing if they had a glucose reading higher than 6.5 mmol/L (confirmed by a secondary measurement, after waiting 20–30 min). Throughout recruitment, 45 participants were randomised, with testing completed by 40 participants due to 3 participants not arriving and 2 participants excluded due to high blood glucose readings. As recommended in the CONSORT reporting guidelines for herbal intervention studies, Figure 1 shows participant flow from enrolment through to analysis. Consistent with other acute studies, 40 participants for a between-group analysis was considered adequately powered to detect a 20% change in task performance. This study has been registered with the Australian New Zealand Clinical Trials Registry (ACTRN12619001425189).

Procedure

This was acute, between subjects double-blind, randomised controlled study conducted at a single centre, involving single administration of either the active herbal extract combination or placebo. Participants attended the research facility on a single day for a period of 2 h with testing taking place between 08:00–12:00 and 13:00–18:00. On testing days, 2 h before their visit, participants were instructed to fast and abstain from consuming any stimulants (e.g. tea, coffee, or caffeine-containing products). Compliance was assessed through self-report before the commencement of session. Each study day comprised of a practice module, a pre-supplement baseline testing session on mood and cognitive measures, followed immediately by a pre-supplement blood glucose measurement, and administration of supplement. A 45-minute absorption time was used based on the average absorption time and pharmacokinetic profile used for the extracts in previous studies [10,17].

Upon attending the appointment, participants self-completed the Positive Affect Negative Affect Scale (PANAS) [18] and Subjective Vitality Scale (SVS) [19] to determine mood at the beginning of the session. Blood glucose and SVS measures were repeated four times each throughout the appointment (both pre- and

Table 1. Participant background demographic and mood measures (*M*, SD).

Variable	Total sample ($N = 40$) *M* (SD)	Active ($n = 21$) *M* (SD)	Placebo ($n = 19$) *M* (SD)	Test statistic
Sex (*n*, %)				$\chi^2 = .00$, $p = .987$
Female	21 (52.5%)	11 (52.4%)	10 (52.6%)	
Male	19 (47.5%)	10 (47.6%)	9 (47.4%)	
Age (Years)	34.46 (12.95)	33.05 (12.53)	35.95 (13.56)	$F = 0.48$, $p = .492$
Education (Years)	15.79 (3.62)	15.60 (3.35)	16.00 (3.92)	$F = 0.12$, $p = .735$
Hours work (Weekly)	23.68 (18.03)	22.84 (16.81)	24.57 (19.66)	$F = 0.09$, $p = .768$
Sick days in past 3 months	1.62 (4.95)	1.05 (1.05)	2.21 (6.94)	$F = 0.53$, $p = .471$
Health rating (compared to others)	1.90 (0.82)	2.1 (0.85)	1.68 (0.75)	$F = 2.61$, $p = .115$
Health rating (compared to a perfect state of health)	2.18 (0.79)	2.35 (0.81)	2.00 (0.75)	$F = 1.96$, $p = .170$
Body Mass Index (BMI)	24.70 (4.35)	24.29 (5.25)	25.12 (3.31)	$F = 0.32$, $p = .572$
Current medical conditions (Yes) (*n*, %)	8 (20.5%)	3 (15.0%)	5 (26.3%)	$\chi^2 = 0.77$, $p = .382$
Current medications (Yes) (*n*, %)	8 (20.5%)	4 (20.0%)	4 (21.1%)	$\chi^2 = 0.01$, $p = .935$
Current supplements (Yes) (*n*, %)	16 (41.0%)	8 (40.0%)	8 (42.1%)	$\chi^2 = 0.02$, $p = .894$
Exercise (Hours per week)	4.55 (3.07)	4.63 (3.85)	4.47 (2.06)	$F = 0.02$, $p = .880$
Alcoholic drinks (in last Week)	4.99 (8.42)	6.95 (8.99)	2.92 (7.47)	$F = 2.34$, $p = .138$
Alcoholic drinks (per session)	3.51 (4.79)	3.33 (2.94)	3.71 (6.26)	$F = 0.62$, $p = .805$
Glasses of water (per day)	6.60 (2.77)	7.13 (3.00)	6.05 (2.48)	$F = 1.47$, $p = .233$
Smoker (Y) (*n*, %)	1 (0.23%)	0 (0.00%)	1 (0.05%)	
DASS Scales				
Depression	19.95 (6.97)	20.00 (5.62)	19.89 (8.31)	$F = 0.00$, $p = .963$
Anxiety	18.72 (5.85)	20.00 (6.49)	17.37 (4.90)	$F = 2.03$, $p = .163$
Stress	24.26 (8.21)	23.60 (6.28)	24.95 (9.99)	$F = 0.26$, $p = .615$
PANAS Scales				
PANAS Positive	32.80 (5.23)	31.67(5.07)	34.05 (5.24)	$F = 2.14$, $p = .152$
PANAS Negative	12.35 (2.80)	12.10 (2.61)	12.63 (3.04)	$F = 0.36$, $p = .552$

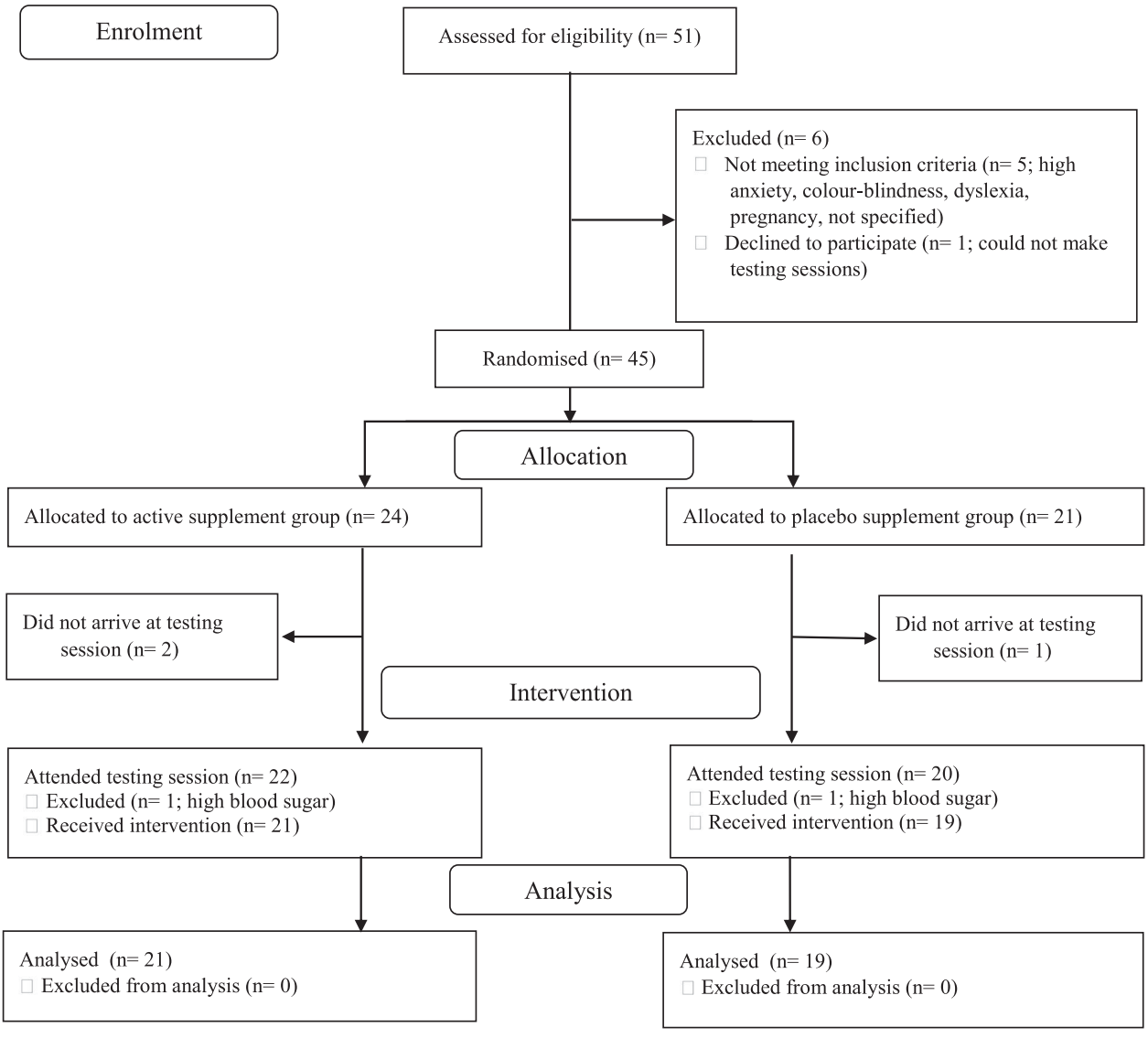

Figure 1. Participant flow diagram.

post- cognitive testing). Cognitive tests were undertaken prior to supplementation and again after the 45-minute rest period post-supplementation. Participant's PFC activity was measured during the cognitive tests via fNIRS and participant's tolerability of the testing was assessed throughout the session. There were no reports of any adverse or intolerance to the study procedures or supplements.

Supplements

The active supplement was made up of commercially available extracts of *Bacopa monnieri* (BM: 150 mg/tablet; Bacognize®), American ginseng *Panax quinquefolieus* (PQ: 50 mg/tablet; Cereboost™) and whole coffee fruit extract (WCFE: 50 mg/tablet; Neurofactor™). Participants consumed a two-tablet dose to provide a total dose of 300 mg BM (2 × 150 mg, which contained 34 mg of bacosides), 100 mg PG (2 × 50 mg, which contained 9 mg of ginsenosides) and 100 mg of WCFE (2 × 50 mg, which contained 40 mg of chlorogenic acid), with a combined active ingredient intake of 500 mg. The placebo supplement was predominately microcrystalline cellulose (581 mg/tablet), to provide a total intake of 1162 mg of cellulose. Supplements were provided by USANA Health Sciences Inc. (Utah, USA) and participants were randomly allocated to consume the supplement (active or placebo) with 200 ml of water. Participants were randomised to supplement conditions at the point of entry to the study, using a random number generator called UX app. To ensure blinding, a research assistant who was otherwise uninvolved in the study assigned participants to one of the supplement conditions via a coding system, linked to the lot numbers

of the containers, which was unknown to the assessor and investigators. The assessor was then informed of the lot numbered bottle to use to then deliver the tablets to the participant following the baseline assessment. The manufacturer retained the identity of the lot numbers in a sealed file until the study was unblinded following data analysis. Both supplements were hard coated tablets matched for red colour, texture and smell.

Measures

Dietary measures

A food frequency measure was used to assess general, habitual dietary intake and specific polyphenol (flavonoid) containing foods, known to influence cognition and well-being, that may have been different between supplement conditions [20,21]. Participants reported the number of days (Not at all, on 1–2 days, on 3–5 days, and on 6–7 days) they consumed a food type (e.g. 'Fruits and berries') and foods rich in flavonoids (e.g. 'Apple') over the past week across 39 items.

Mood measures

Participants were given three measures of mood and one of tolerability to better understand the potential impact of mood states on cognitive test performance.

Depression Anxiety and Stress Scale-21 (DASS-21). The DASS 21-item version [22] assessed three negative affective states, depression, anxiety and stress, experiences over the past week, prior to testing day. Participants rated statements such as 'I found it hard to wind down' on a four-point scale with 0 = Did not apply to me at all, to 3 = Applied to me very much, or most of the time. Scores are summed for each affective state.

Positive Affect Negative Affect Scale (PANAS). The PANAS consists of 20 affective descriptors (e.g. 'enthusiastic', 'jittery') [18]. For each descriptor, participants rate on a 5-point scale from 1 (Very slightly or not at all) to 5 (Extremely) the extent to which they have experienced the described affective state during the past few weeks. For this study, a researched variation of 'today' was used. 'Positive affect' and 'negative affect' subscale scores were obtained by summing the 10 positive and 10 negative item scores, respectively.

Subjective Vitality Scale (SVS). The SVS is a measure of psychological well-being consisting of six items regarding aliveness and energy (e.g. 'I have energy and spirit.') [19]. Participants rated each item on a scale from 1 (Not at all true) to 7 (Very true). A mean score across all items was computed.

Tolerability. Tolerability was assessed via monitoring of unsolicited questions (e.g. 'How have you been feeling?'), to elicit reports of any experience of adverse events throughout the appointment.

Blood glucose measurement

Blood glucose tests were undertaken via AccuChek Performa glucometer, test strips and single-use Lancet Safe-T-Pro Plus lancets (Roche, Castle Hill, NSW). The Accu-Chek Performa glucometer has been shown to meet the accuracy and reliability standards for glucose testing [23].

Cognitive measures

The cognitive test battery was created and conducted using Eprime3 (Psychology Software Tools, Pittsburgh, PA) to assess working memory (n-back tasks), selective attention and inhibition (Stroop, Go/No-go, 1 and 2 choice reaction time tasks), which have been shown to be sensitive to fNIRS responses. The first task presented to participants was always the 1-back task to ensure participants familiarity with n-back tasks and to increase the likelihood of participants conducting the 2- and 3-back tests correctly. The last task was the 1- and 2-choice reaction time test, with the other tests pseudo-randomised in between. To accommodate for fNIRS measures during cognitive testing, a block design paradigm was used such that all cognitive tests had four 'active' blocks lasting at least 30 s, with rest blocks, lasting 25–30 s, spaced in between.

N-back tasks. All N-back tasks were comprised of letters from 'A' to 'J' with a correct match appearing 25% of the time. Each work block consisted of 15 letters presented on the screen for 500 msec with 1500 msec separating the presentation of each letter. When participants saw a correct match, they were instructed to press the spacebar, otherwise, no key was to be pressed. Response time, accuracy and error scores were obtained for each work block tasks and averaged to give an overall score and response time for 1-back, 2-back and 3-back tasks.

Go-No-Go task. The Go-No-Go task was comprised of a block of all 'Go' stimuli (which acted as the rest block for fNIRS analysis purposes), followed by a block of 'No-Go' and 'Go' stimuli. The 'Go' stimuli were represented by a blue circle, the 'No-Go' stimuli by a grey circle and when the 'Go' stimulus appeared participants were instructed to press the spacebar as quickly and accurately as possible. In the Go-No-Go blocks, the 'No-Go' stimuli were presented 30% of the time as this has been found to require a higher amount of inhibitory control and subsequently a higher cognitive demand [24]. Stimuli were presented for a maximum of 500 msec with 500 msec in between each stimulus presented, with 30 stimuli presented in each work block.

Stroop task. For the Stroop task, the congruent Stroop acted as the 'rest' block and the incongruent Stroop the 'active' blocks for fNIRS analysis purposes. For the congruent Stroop task, the words yellow, blue, green or red were presented to participants and were written in their correct respective colours. When presented with a stimulus, participants had to respond by pressing the correct arrow key (keys were labelled with the four separate colours). Thirty stimuli were randomly presented in each work block with an approximately even number of stimuli from each word/colour. Each stimulus was present on the screen until participants pressed a key, with 1000 msec between each stimulus. The same test parameters were used in the incongruent part of the task, except the word that appeared was never written in its respective colour and instead was randomly presented as one of the other three respective colours. Participants were instructed to press the arrow key that matched the colour of the word (keys were colour coded accordingly) and not what the word said. Before the actual task begun a short practice was provided to participants to familiarise them with the task.

Reaction time. The reaction time test consisted of a 1-choice task acting as the 'rest' block for fNIRS purposes and the 2-choice reaction time test as the 'work' blocks. For the 1-choice task participants were instructed to press the spacebar as quick as possible when the black square appeared on the screen. For the 2-choice either a blue or red circle was presented with participants instructed to press the corresponding arrow key (keys were colour coded accordingly). Each work block consisted of 12 stimuli that appeared at random time intervals to avoid participants anticipating the appearance of the next stimuli. 2-Choice stimuli were evenly distributed between blue and red circles and were randomly presented.

Response time and accuracy score. For the Stroop and Go/no-go tasks, an inverse efficiency score (IES) was calculated to better understand the speed and accuracy trade off in completing the task. The formula is as follows: IES = RT/PC (RT = reaction time in msec, PC = percentage correct in decimals) [25]. The score provides an estimate of the overall speed of attention. A lower score indicates better performance as for each accurate response there is a quicker response time. Conversely, a higher score means that the response time is longer for each accurate response.

Functional near-infrared spectroscopy (fNIRS) setup, data collection and processing

The fundamental basis for fNIRS is that most biological tissue such as skin and bone are transparent to NIR light, while O_2Hb and HHb are better absorbers of NIR light in the spectrum of 700–900 nm. The principle of fNIRS is based on the absorption rate of O_2Hb and HHb using the modified Beer–Lambert law (MBLL) at two different wavelengths of NIR light between transmitter (Tx)–receiver (Rx) pairs placed over the scalp. Therefore, brain maps can be developed by spatially arranging the NIR light Tx–Rx pairs on the head so that specific brain region(s) of interest can be determined [26]. In this study, an eight-channel (four channels on each hemisphere) continuous-wave NIRS system (Octamon, Artinis Medical Systems, The Netherlands) was placed over the PFC to measure fNIRS signals using two wavelengths at 750 and 850 nm during the cognitive testing battery. Before beginning the cognitive tests, optodes were digitised using the Polhemus Patriot (Polhemus, Colchester, VT, USA).

For each participant, an individual differential pathlength factor (DPF) was used to account for age differences [27]. All signals were sampled at a rate of 10 Hz. All raw data were exported into a MATLAB-based analysis package (HOMER2) and analysed using the following analysis pipeline. Firstly all raw data converted to changes in optical density (OD) [28]. Channels with low signal-to-noise ratio were removed using the 'enPruneChannels' function. As all channels displayed an excellent signal-to-noise ratio, none of the channels were excluded from the analysis. A motion artefact detection algorithm (hmrMotionArtifactByChannel; AMPThresh = 0.40, SDThresh = 5.0, tMotion = 0.5 and tMask = 1.0) was then used to identify motion artefacts on a channel-by-channel basis that exceed the pre-specified thresholds in the OD time-series. After motion artefact identification was performed, a motion artefact correction method using the principal component analysis (PCA) filter was applied to any active channel that exhibited a signal change greater than the pre-specified thresholds (hmrMotionArtifactPCArecurse; AMPThresh = 0.40, SDThresh = 5.0, tMotion = 0.5, tMask = 1.0, nSV = 0.97 and maxIter = 5). A bandpass filter (hmrBandpassFilt; high-pass = 0.01 and low-pass = 0.50) was then applied to filter out low or high frequency noise. The OD data were then converted into concentration changes using the MBLL using the 'hmrOD2Conc' function (ppf = 6.0, 6.0) and block averaged (hmrBlockAvg; trange = −5.0, 25.0) to provide an indication of an average change of four trials for all eight channels during each sensory condition. To visualise the changes in O_2Hb over time (pre vs. post) and condition (active vs. placebo), an open-source MATLAB-based toolbox (Atlasviewer) was used [29]. Atlasviewer uses the pre-processed data from HOMER2, in conjunction with digitised probe-set coordinates of optodes to general anatomical spatial maps.

The change in haemodynamic response for the left and right PFC were averaged to determine hemispheric differences in cortical activation between conditions. Additionally, to determine hemispheric lateralisation, a Laterality Index of O_2Hb, as described by Seghier [30] for fMRI studies, was calculated for all conditions in young and older adults. The formula used to calculate the Laterality Index is as follows

$$\text{Laterality index} = \frac{\text{Left PFC} - \text{Right PFC}}{\text{Left PFC} + \text{Right PFC}}.$$

Based on the formula above, negative values up to −1 indicated right PFC dominance while positive values up to +1 indicated left PFC dominance.

Statistical analysis

Data from the fNIRS were exported into Matlab (The MathWorks, Inc, Natick, MA) and analysed in the Homer2 plugin toolkit. Data from the cognitive battery were transferred from Eprime3 (Psychology Software Tools, Pittsburgh, PA) to IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY, USA) for analysis alongside data from fNIRS, background health and demographic measures, PANAS, SVS and blood glucose measures.

Pearson's Chi-Square and ANOVA analyses assessed participant's background demographics, dietary behaviours, DASS and PANAS scores (Table 1; dietary behaviours not shown). Subtracting pre-supplementation cognitive scores from post-supplementation scores for the cognitive and fNIRS measures created change scores. ANOVA analyses tested for change in performance between supplement conditions.

Results

Demographic background and mood measures

All background measures of mood, demographics, self-reported health and dietary intake of flavanoids were considered as potential covariates to any supplement effects. There were no significant differences between supplement conditions in background demographic or dietary measures (See Table 1), so they were not used as covariates to the assessment of supplement effects. Data for dietary intake of polyphenol (flavonoid) rich foods not shown.

Blood glucose and SVS measures

There were no significant differences between supplement conditions for measures of blood glucose throughout the testing sessions, nor any reported change in subjective vitality experiences throughout the testing sessions. Table 2 shows the means and standard deviations for each supplement condition at each time point.

Baseline, pre-supplementation cognitive measures

There was a significant difference between supplement groups for the 3-back response time (RT) at baseline, with the active group taking longer than the placebo group, $F(1, 38) = 5.84$, $p < .05$, mean scores shown in Table 3. No other significant differences were identified between groups for pre-supplementation baseline measures. Baseline 3-back RT was used as a covariate in the analysis of post-supplement change scores in response time.

Post-supplement change score cognitive measures

Working memory

Those in the active supplement condition, compared to placebo, showed significantly improved response time on the 2-back task ($p < .05$) and improved 3-back accuracy performance ($p < .01$, see Table 3), with an overall Cohen's d effect size of 0.67–0.89, respectively. For the number of errors made during task performance, there were marginally insignificant fewer errors made (hitting the space bar incorrectly) on 1-back performance by those in the active supplement condition compared to placebo ($p = .052$). Whereas there were significantly fewer errors made on 2-back task performance for those in the active supplement condition compared to placebo ($p < .01$).

Table 2. Blood glucose and SVS measures for supplement conditions, presented as mean (SD).

	Subjective vitality scale scores ($N = 40$)				Blood glucose (mmol/L) ($N = 40$)			
	Baseline cognitive testing		Post-supp cognitive testing		Baseline cognitive testing		Post-supp cognitive testing	
	Pre-test	Post-test	Post-test	Pre-test	Pre-test	Post-test	Post-test	Pre-test
Active	4.82 (1.01)	4.57 (1.33)	4.87 (1.10)	4.52 (1.21)	5.18 (0.48)	5.38 (0.59)	5.07 (0.44)	4.89 (0.50)
Placebo	4.93 (0.97)	4.31 (1.54)	4.91 (1.22)	4.17 (1.36)	5.10 (0.49)	5.13 (0.47)	5.01 (0.54)	4.92 (0.44)

Note: supp: supplement.

Table 3. Baseline and change scores for cognitive performance measures by supplement condition, presented as mean (SD).

Cognitive measure	N	Baseline scores		Post-supplement change scores		F ratio, p-Value	Cohen's d
		Active (N = 21)	Placebo (N = 19)	Active	Placebo		
1-Back Response Time (msec)	40	563.13 (92.55)	567.89 (74.38)	−11.09 (155.52)	12.31 (112.56)	0.29, $p = .592$	0.17
1-Back Accuracy (%)	40	92.63 (9.95)	92.44 (9.05)	−0.16 (13.64)	−1.35 (11.99)	0.08, $p = .771$	0.08
1-Back Error (*n*)	40	1.05 (1.28)	1.00 (1.11)	−0.43 (1.36)	0.58 (1.80)	4.01, $p = .052$	0.65
2-Back Response Time (msec)	40	752.24 (73.20)	710.56 (125.82)	**−55.05 (121.01)**	**35.15 (152.75)**	**4.32, $p = .044$**	**0.67**
2-Back Accuracy (%)	40	83.27 (11.81)	84.00 (16.42)	6.44 (11.93)	−3.96 (20.88)	3.83, $p = .057$	0.63
2-Back Error (*n*)	40	2.33 (1.43)	1.89 (1.76)	**−0.81 (1.40)**	**1.28 (3.20)**	**7.43, $p = .010$**	**0.88**
3-Back Response Time (msec)	40	824.49 (87.46)	762.86 (72.17)*	−48.45 (119.90)	30.24 (117.14)	0.36, $p = .551$	0.20
3-Back Accuracy (%)	40	69.29 (16.26)	76.53 (14.01)	**10.34 (18.41)**	**−6.18 (19.93)**	**7.69, $p = .009$**	**0.89**
3-Back Error (*n*)	40	3.19 (1.40)	3.32 (1.77)	−0.90 (1.87)	−0.68 (2.19)	0.11, $p = .733$	0.10
Go-No-Go Response time (msec)	40	367.55 (55.31)	345.38 (32.88)	−5.52 (67.28)	25.80 (48.86)	2.78, $p = .103$	0.54
Go-No-Go Accuracy (%) (inhibited)	40	88.02 (9.02)	88.68 (10.10)	2.74 (10.68)	1.90 (6.16)	0.91, $p = .764$	0.08
Go-No-Go IES[a]	40	421.45 (76.08)	392.91 (43.49)	−20.76 (98.48)	18.64 (64.85)	2.18, $p = .148$	0.47
Stroop Test – Congruent Response time (msec)	40	693.89 (152.06)	648.17 (82.79)	−150.58 (161.52)	−72.23 (69.28)	3.82, $p = .058$	0.63
Stroop Test – Congruent Accuracy (%)	40	93.63 (5.72)	96.38 (4.79)	2.37 (4.62)	0.65 (3.94)	1.60, $p = .214$	0.40
Stroop Test – Congruent IES[a]	40	742.53 (159.60)	672.72 (78.83)	**−177.90 (178.57)**	**−80.98 (93.42)**	**4.47, $p = .041$**	**0.68**
Stroop Test – Incongruent Response time (msec)	40	813.44 (152.17)	786.40 (113.42)	−79.65 (158.14)	−87.46 (94.76)	0.03, $p = .853$	0.06
Stroop Test – Incongruent Accuracy (%)	40	95.51 (4.18)	96.46 (3.34)	−2.50 (4.83)	−0.34 (3.56)	2.54, $p = .119$	0.51
Stroop Test – Incongruent IES[a]	40	855.02 (172.80)	817.19 (130.33)	−55.16 (203.34)	−89.20 (114.94)	0.41, $p = .525$	0.21
1-Choice Response time (msec)	40	317.00 (38.29)	325.62 (38.13)	12.09 (63.38)	13.11 (33.80)	0.00, $p = .950$	0.01
2-Choice Response time (msec)	40	464.22 (87.66)	480.79 (63.99)	18.74 (95.23)	9.77 (58.42)	0.15, $p = .725$	0.10
2-Choice Accuracy (%)	40	95.26 (3.97)	94.08 (6.74)	1.20 (3.29)	1.47 (4.62)	0.04, $p = .835$	0.06

[a]IES: Inverse efficiency score.
*$p \leq .05$.

Speed of attention and inhibition

The IES for the Stroop (congruent) response time showed there was a significant improvement ($p < .05$) in an overall efficiency of task performance for those in the active supplement condition compared to those in placebo. For every accurate response made in the congruent task, those in the active supplement condition were able to perform the tasks with the quicker response time. There were no other significant differences on incongruent Stroop scores, as a measure of attention, in either response accuracy or response time.

fNIRS change from baseline measure by supplement condition

Significant differences in fNIRS change score were observed in left and right PFC, with the 3-back task resulting in less activation for the active supplement condition compared to placebo in both the right ($p < .001$) and left ($p < .01$) hemispheres (See Table 4). There was significantly less activation in the left PFC for the active supplement condition compared to placebo for incongruent Stroop accuracy ($p < .05$). No other significant differences between supplement conditions were observed for Laterality Index or other cognitive tasks.

Taken together the overall patterns of results show improved accuracy and response time across tasks of cognitively demanding working memory tasks following active treatment. Shown in Figure 2, the performance of the 3-back task is associated with less activation across the left and right prefrontal cortex during the most demanding and cognitively effortful task for those in the active supplement condition compared to placebo.

Table 4. Change score in fNIRS response (μM) according to left and right PFC and Laterality Index for accuracy score of each cognitive task.

	RPFC[a]		LPFC[b]		LI[c]	
	Active	Placebo	Active	Placebo	Active	Placebo
1-Back	−0.15 (0.27)	−0.02 (0.16)	−0.12 (0.21)	0.00 (0.17)	0.01 (0.36)	0.02 (0.26)
2-Back	−0.07 (0.20)	0.05 (−.20)	−0.08 (0.19)	0.03 (0.29)	−0.08 (0.25)	−0.14 (0.31)
3-Back	**−0.13 (0.26)**	**0.23 (0.29)*****	**−0.03 (0.21)**	**0.19 (0.26)****	0.18 (0.28)	0.00 (0.34)
Go-No-Go	−0.11 (0.13)	−0.12 (0.34)	−0.09 (0.11)	−0.10 (0.36)	0.08 (0.42)	0.03 (0.39)
Stroop test – Congruent	−0.01 (0.07)	−0.07 (0.27)	−0.02 (0.08)	−0.00 (0.44)	0.00 (0.46)	0.16 (0.41)
Stroop test – Incongruent	−0.06 (0.17)	0.00 (0.13)	**−0.14 (0.22)**	**0.00 (0.11)***	−0.14 (0.42)	0.00 (0.36)
2-Choice	−0.00 (0.12)	0.05 (0.30)	0.02 (0.11)	0.05 (0.21)	0.01 (0.32)	0.10 (0.38)

[a]RPFC: right prefrontal cortex; [b]LPFC: left prefrontal cortex; [c]LI: Laterality Index.
*$p \leq .05$; **$p \leq .01$; ***$p \leq .001$.

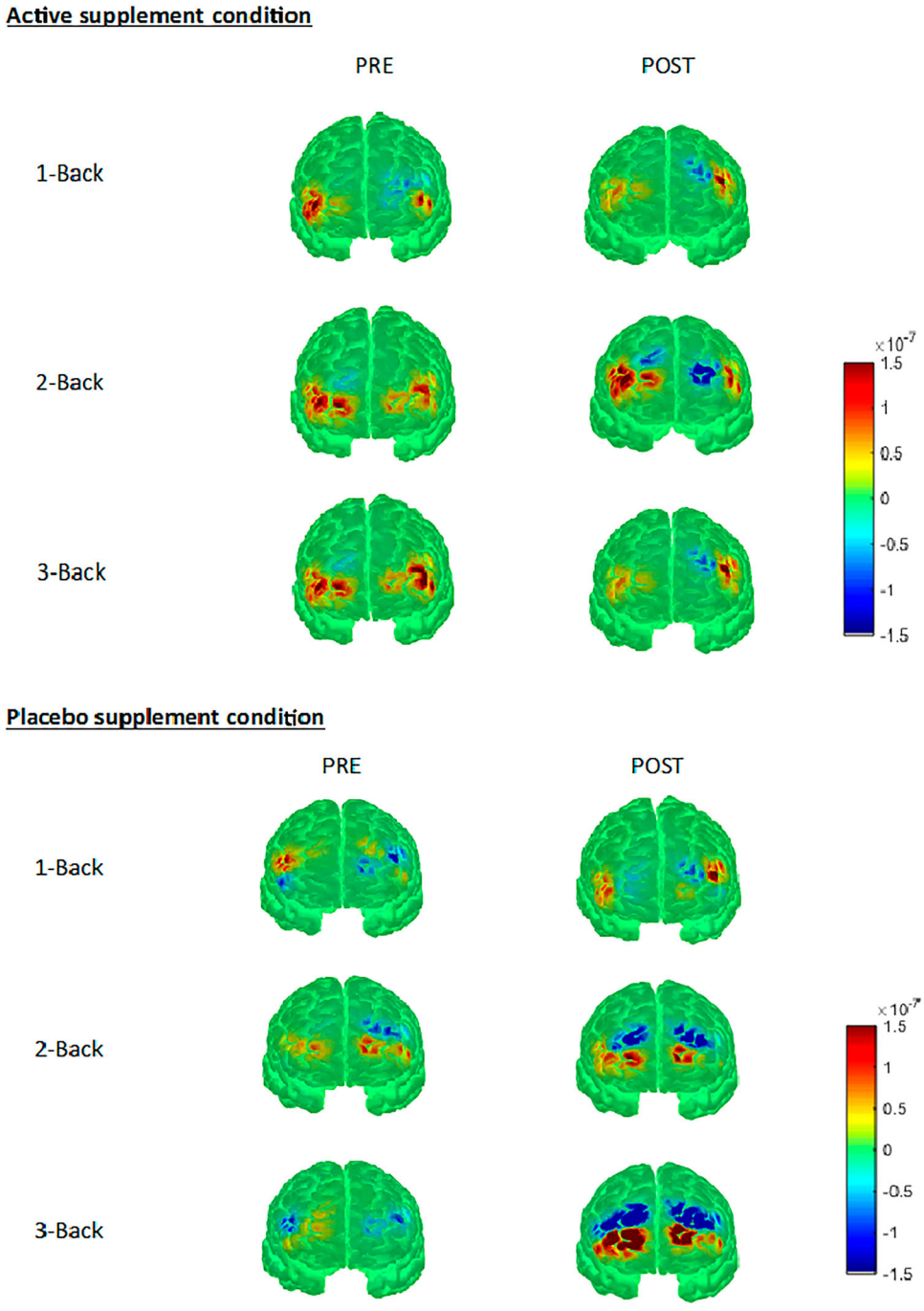

Figure 2. Activation patterns of the left and right PFC during pre and post intervention by supplement condition on the n-back task.

Discussion

The current study demonstrated that a single, combined dose of herbal extracts known to influence cognitive function elicited improved working memory performance but not on tasks of attention compared to placebo, despite an overall increase in efficiency for response time. Further, this was the first study to examine the combined dose effects of Bacopa, ginseng and whole coffee fruit extracts on cognitive performance and brain activation of the PFC using fNIRS. Importantly, the results show clearly that the combination can modulate brain activation and cognitive task performance, and show reduced activation of the PFC related to effortful mental demand, reflecting increased neural efficiency concomitant with improved cognitive performance. This is the first report of acute, significant changes in cognitive function following intake of a combined, multi-ingredient herbal supplement with concomitant observed changes in haemodynamic response in healthy adults.

The combination of extracts makes it difficult to determine the potential mechanism of effect underpinning improved task performance and neural efficiency. To date, no published studies have investigated the potential synergistic effects of these active ingredients on brain activity. It is worth noting that the biological mechanisms of action are still poorly understood. Based on the primary active polyphenolic constituents of each ingredient, known to possess psychoactive properties and mechanisms of action on the central nervous system, it is plausible that some beneficial, synergistic effect is being demonstrated. This is particularly worth considering when the dose of each ingredient used within the combination is examined against known dose and time effects of each ingredient. For example, an acute study of Bacopa [7] showed change from baseline improvement on Stroop performance at 1 and 2 h post 640 mg dose of BM, and at 1 h post 320 mg BM dose compared to placebo. In contrast, this study used 300 mg of BM, a lower dose compared to the previous study, with positive effects still found on a working memory task. Similarly, a single dose of 200 mg of ginseng (Cereboost TM) improved working memory performance 3 h post dose in healthy middle-aged adults in the absence of mood effects [31], whilst the current study demonstrates improved working memory performance with only 100 mg dose of ginseng in the combination with the other extracts. It should be pointed out that the 100 mg dose in combination with other extracts did not result in increases in attention task performance as seen in previous research [9]. Given the dose used in the current study is less than what has been used previously, the 100 mg of ginseng as a component of the whole supplement is unlikely to have produced effects on working memory alone. A Cohen's d effect size of 0.89, 1 h post dose between-group differences on the 3-back working memory task, suggests that the synergy of the components in the supplement are having a much larger effect when comparative effects size for ginseng intake alone are examined. For example, in previous research, the effect size for improved 3-back task response following an acute 200 mg dose of ginseng, 4 h post dose is Cohens' *d* of 0.25 [17].

In conjunction with cognitive performance measures, this study also explored changes in the activation of brain regions related to effortful mental demand. The results show reduced activation across the brain hemispheres for those in the active treatment condition compared to placebo, whilst still maintaining improved working memory task accuracy. The PFC plays an important role in the processing of memory and associated workload. The current finding is novel as this is the first report of changes in cognitive function following intake of a combined, multi-ingredient herbal supplement in concert with observed changes in hemodynamic response and activation changes in both the right and left PFC in healthy adults. Further, the changes in fNIRS response related to performance on the n-back task replicate previous research that shows participant mental workload across the 1-, 2- and 3-back tasks can be differentiated [32].

This pilot study demonstrates novel, acute improvements of working memory during a cognitively demanding battery following herbal supplementation compared to placebo. This study also demonstrates the feasibility and sensitivity of fNIRS in determining PFC activation related to task performance following a nutritional intervention. However, the results should be interpreted with some caution. First, this is the first investigation (to our knowledge) of a combined extract formulation on neurocognitive function, and this study needs replication with a more specific focus on diverse working memory tasks. Second, the pattern of findings and trend towards statistically significant differences between conditions on tasks of working memory suggests that a larger sample size would usefully quantify the magnitude of the effect. Finally, methodologically it would be useful to narrow the age range to better differentiate task performance and potential beneficial effects for cognitive performance related to cognitive ageing. It is highly probable that effects may be more pronounced in middle-aged adults where the everyday reduction of cognitive resources due to the aging brain may be more acutely impacted by the combined extracts. Consequently, comparison of cognitive performance changes in older vs younger adults would be useful to increase the understanding of cognitive performance and metabolic activation in the brain.

In conclusion, future studies should replicate the current findings and examine potential positive effects on neurocognitive function across different cognitive domains, with a focus on working memory tasks. Whilst there may be different mechanisms of action for each substance in the combination of extracts, considering an underlying mechanism that might influence specific brain regions may be more useful. Further, comparing dose, time of testing and age of healthy adults in future research could then determine potential 'peak' times and dose for acute beneficial effects utilising fNIRS as a sensitive measure to qualify the brain regions benefiting from consumption in more detail. Chronic intake studies would also be useful to determine whether there are any sustained long-term gains for performance and brain activation.

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