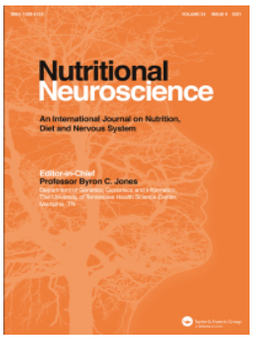

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Effects of blackcurrant juice on pre-frontal cortical haemodynamics and cognition in healthy young adults

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ABSTRACT

Background: Evidence from randomised controlled trials demonstrates the modulatory effects of polyphenol consumption on the vascular system including improvements to cortical blood flow (CBF), microvascular blood flow, and large artery plasticity. Polyphenol-rich blackcurrants have been shown to inhibit monoamine oxidase, modulate brainwave spectral activity and modulate peripheral blood flow. This study assessed whether blackcurrant consumption can modulate blood flow in the shallow pre-frontal cortex, as measured using near infrared spectroscopy, during rest and under cognitive demand.

Methods: A randomised double blind, placebo-controlled balanced cross over design was used to assess the efficacy of a cold pressed blackcurrant juice drink (Blackadder cultivar, Neuroberry, Plant and Food Research Ltd.) standardised at 500 mg of total polyphenols upon attention and working memory and prefrontal cortical haemodynamics at rest and during cognitive load in 20 healthy young adults aged 18–35 years, following a 60-minute absorption period.

Results: Consumption of the Blackadder juice extract resulted in significant acute modulations of pre-frontal cortex haemodynamics during resting absorption and cognitive task performance as indicated by a decrease in deoxygenated haemoglobin [$F(1,19) = 5.70$, $p = 0.027$] and an increase in left hemisphere oxygenated haemoglobin during task performance [$F(1.88,33.83) = 7.70$, $p = 0.002$]. No effects on cognition were observed in this sample of healthy young adults.

Conclusion: Results from this trial outline the ability of a blackcurrant juice extract to increase cerebral blood flow during cognitive demand in healthy young adults. The effects of the juice extract in addition to other types of blackcurrant extracts upon acute and chronic brain function and blood flow deserve further investigation.

Trial registration: ClinicalTrials.gov identifier: NCT01540123.

KEYWORDS
Blackcurrant; polyphenols; monoamine oxidase; cortical blood flow; cognition; near infrared spectroscopy

Introduction

During natural ageing, cerebral blood flow reduces by up to 0.5% per year [1,2]. Preservation of blood flow, including the maintenance of endothelial function, is inversely associated with the incidence of cardiovascular disease (CVD) [3], mild cognitive impairment [4], and cognitive decline in patients with vascular cognitive impairment [5]. Epidemiological observations suggest that nutrition plays a role in the maintenance of the cardiovascular system with the consumption of phytochemicals inversely correlated to the incidence of CVD risk factors [6,7]. Evidence from randomised controlled trials demonstrates the modulatory effects of polyphenol consumption on the vascular system including improvements to cortical blood flow (CBF), microvascular blood flow, and large artery plasticity, with differing effects of specific phenolic compounds and doses, and multiple mechanisms proposed for these modulatory effects including upregulation of nitric

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oxide secretion, anti-inflammatory actions, modulation of gut microbiota and interaction with intra – and inter-cellular signalling pathways (See Grosso et al. [8], Joris et al. [9], Woodward et al. [10] and Fraga et al. [11] for reviews.)

Blackcurrants have received attention over the past decade as a source of polyphenols, with a focus on anthocyanins and their potential impact upon human vascular and cognitive function. Published human intervention studies pertaining to blackcurrants and blood flow have focused upon peripheral blood flow with varying outcomes. Blackcurrant extract containing 105 mg of anthocyanins elicited reductions in systolic and diastolic blood pressure [12,13] and decreased carotid–femoral pulse-wave velocity [13] in older adults following 7 days' supplementation. In endurance trained males, 7 days' supplementation of a blackcurrant extract with 138.6 mg of anthocyanins produced increases to stroke volume and cardiac output, and decreased total peripheral resistance, with no changes to heart rate or blood pressure [14]. Similarly, acute intervention with blackcurrant containing 172 mg anthocyanins increased forearm blood flow and reduced resistance, but did not impact blood pressure or plasma nitrate, nitrite, or endothelian-1 [15]. Our previous papers outline the acute impact of blackcurrant consumption upon cognitive performance in healthy young adults, after sustained mental performance [16] and modulation of brain wave spectral activity in healthy young volunteers [17]. Furthermore, inhibition of monoamine oxidase in-vivo and modulation of monoaminergic tone were seen to be affected after supplementation with blackcurrant juice [16,18]. The molecule responsible for the inhibition of monoamine oxidase in blackcurrants has recently been identified as sarmentosin [19].

Studies of cognitive effects of blackcurrants are limited but their potential to exert effects is supported by numerous studies of anthocyanin-rich blueberries, with cognitive benefits shown following both acute and chronic consumption [20], and indication of a link between increased brain perfusion and cognitive benefits following 12 weeks' consumption [21]. Acute effects of polyphenol-rich interventions on cerebral haemodynamics have also been shown following consumption of Sideritis scardica [22] cocoa [23,24] and flavanone-rich citrus juice [25] but a concomitant improvement to cognition has not been observed in the limited number of studies to assess it, potentially due to ceiling effects [23] or use of interventions not shown to produce acute cognitive benefits [26]. Interestingly, Gratton et al. [27] showed that that consuming ~681 mg of cocoa flavanols lead to more efficient tissue oxygenation responses in frontal areas of the brain during a CO2-challenge in healthy young individuals as measured by fNIRS. Only individuals who benefited from flavanol intake during hypercapnia experienced cognitive benefits during a modified Stroop test, suggesting that these effects are possibly linked.

The current study will assess the effects of blackcurrant on cerebral haemodynamics for the first time, and further explore any cognitive benefits. A blackcurrant nutritional intervention, such as the Blackadder juice extract (containing 415 mg anthocyanins) shown in our previous papers [16,18] to modulate neurotransmitter tone, which plays a key role in vasodilatation and the regulation of cerebral blood flow [28], could impact cerebral blood flow on two levels, regulating endothelial-dependent nitric oxide and via a direct effect upon neurotransmitter tone. The study will use Near Infrared Spectroscopy (NIRS) to assess shallow pre-frontal cortical haemodynamics under cognitive demand, and at rest, utilising cognitive paradigms focusing upon central executive tasks and attention processing which have been shown to elicit an intervention-dependent cerebral blood flow response in the frontal cortex [29–31]. We hypothesise that consuming blackcurrant juice will increase shallow cerebral blood flow when compared to control during performance of a cognitive demand battery designed to induce cerebral activation in the shallow prefrontal cortex.

Materials and methods

Design

The acute effects of a single serving of Blackadder blackcurrant juice drink standardised to contain 500 mg of polyphenols per 60 kg of body weight versus a sugar matched control on pre-frontal cortical haemodynamics and cognition were investigated. Drinks were matched for volume, taste, appearance and sugars but differed in the amount of total polyphenols and other unmeasured constituents in the blackcurrants such as water soluble vitamins. The study followed a double-blind, counterbalanced, placebo controlled, repeated measures design. Participants were randomly allocated to treatment orders as selected through a Williams Latin Square [32]. The trial was registered on clinicaltrials.gov ref NCT01540123.

A recruitment target of 20 participants was set based on the numbers of participants published in previous studies using a similar paradigm which showed the effects of nutritional supplements on blood flow in the shallow prefrontal cortex as measured by NIRS [29,33]. As the project was powered based on the primary outcome, participant numbers may not be sufficient to detect changes in other outcomes such as cognitive performance.

Participants

Participants were recruited using opportunity sampling from the Newcastle Upon-Tyne, UK area. Participants received £35 to recompense them for any expense they may have incurred to participate in the trial. Prior to acceptance onto the study, potential participants attended a one-hour training session. During this training session participants gave their informed consent to participate and were screened for any contra-indications to the study with the use of an exclusion questionnaire. Exclusion criteria included: Diagnosed history of any psychiatric disorder, aged under 18 or over 35 years, user of tobacco or nicotine containing products, BMI above 30 kg/m2 or below 17 kg/m2, diagnosis of diabetes, current use of prescription, over-the-counter or recreational drugs, an English language comprehension which is not equal to a native English speaker and any eyesight issue which cannot be corrected through the use of spectacles or contact lenses.

Participants then completed four repetitions of the study day tasks to ensure they met the required minimum standards to participate in the study and to alleviate practice associated effects [34,35]. Mean data for each test and practice repetition can be found in supplementary data Table 1.

The study received ethical approval from the Northumbria University School of Life Sciences Ethics Committee (RE20-10-11208) and was conducted according to the Declaration of Helsinki.

Treatments

Participants received two intervention drinks containing either 0 mg of polyphenols (control) or 500 mg polyphenols per 60 kg of body weight (8.3 mg polyphenols/ kg BW) in the form of a 142 ml of cold pressed blackcurrant juice (Blackadder cultivar, Neuroberry®, cultivated and processed by Plant and Food Research Ltd, New Zealand (Blackadder Juice)). The Blackadder juice was assessed for the phytochemical constituents using the method described by Schrage et al. [36]. The major phytochemicals found in the crude juice can be found in Table 1 and average and range doses can be found in Table 2.

In each case, drinks comprised of 3.44 g of glucose (57.3 mg/kg bw), 4.63 g of fructose (77.2 mg/kg bw), 0.8 g (13 mg/kg bw) of sucrose, 6 g (100 mg/kg bw) of sucralose sweetener (Splenda™) and 50 ml (0.84 ml/kg bw) of blackcurrant flavouring (Schweppes blackcurrant cordial). The total volume of the drink was

Table 1. Phytochemical constituents of 'Blackadder' blackcurrant juice (mg/100 mL of raw juice and mg supplemented per 60 kg of body weight).

Compound	Quantity (mg/100 ml)	Quantity (mg/60 kg)
Caffeoyl Quinate	6	4.7
Caffeic acid Glucoside	2.5	2.0
pCoumaroyl Quinate	5.7	4.5
Epigallocatechin	4.9	3.9
Delphinidin Glucoside	47.7	37.7
Delphinidin Rutinoside	184.6	145.9
Cyanidin Glucoside	20.6	16.3
Cyanidin Rutinocide	206.5	163.2
Unidentified Anthocyanin	3.5	2.8
Unidentified Anthocyanin	3.7	2.9
Unidentified Anthocyanin	5.4	4.3
Myricetin Rutinoside	15.3	12.1
Myricetin Glucoside	2.2	1.7
Rutin = Quercetin Rut	3.6	2.8
Quercetin Glucoside	2	1.6
Quercetin pentoside	1.7	1.3
Myricetin	2.2	1.7

Table 2. Anthocyanins and other phenolic compounds in each of the treatment conditions (mg per kilo of body weight, average dose given (mg) and dose range (mg)).

	Control	Blackadder
Anthocyanins (mg/kg)	0	6.21
Anthocyanin average dose (mg)	0	415
Anthocyanin dose range (mg)	0	294–594
Other polyphenols (mg/kg)	0	2.11
Other polyphenols average dose (mg)	0	141
Other polyphenols dose range (mg)	0	100–202
total polyphenols (mg/kg)	0	8.33
Total polyphenols average dose (mg)	0	556
Total polyphenols dose range (mg)	0	395–798

made up to 200 ml (3.34 ml/kg) with water Drinks were coded and prepared freshly from frozen each morning by a third party who had no further part in the running of the study. No member of the investigation team was aware of the coding of the drinks until a blind-data review was completed. Drinks were served chilled in an opaque brown bottle by an independent third party. All quantities discussed are based on a 60 kg person, drink quantities were calculated per kilogram of body weight.

Cognitive and mood measures

All cognitive measures and mood scales were delivered using the Computerised Mental Performance Assessment System (COMPASS, Northumbria University, Newcastle upon Tyne, UK).

A modified version of the 60 min cognitive demand battery (CDB) [37] was used to assess NIRS outcomes during cognitive demand. The modified cognitive demand battery lasted 30 minutes and involved three repetitions of the nine-minute battery, consisting of serial 3 subtractions, serial 7 subtractions and rapid visual information processing followed by a mental fatigue visual analogue scale. This version of the CDB has been shown to activate the pre-frontal cortex in brain imaging studies [30].

Serial threes subtraction task

Computerised versions of the serial subtraction tasks were implemented using tests of 2-minute duration. Participants were required to count backwards in threes from a given number as quickly and as accurately as possible using the number keys to enter each response. A random starting number between 800 and 999 was presented on the computer screen, which was cleared by the entry of the first response. The task was scored for number of responses, number of correct responses and number of errors. In the case of incorrect responses subsequent responses were scored as positive if they were scored as correct in relation to the new number.

Serial 7 subtractions

This was identical to the Serial threes task except that it involved serial subtraction of sevens.

Rapid visual information processing

The participant was required to monitor a continuous series of digits for targets of three consecutive odd or three consecutive even single digits. The single digits were presented at the rate of 100 per minute and the participant responded to the detection of a target string by pressing the space bar on the computer keyboard as quickly as possible. The task was continuous and lasted for 5 minutes, with 8 correct target strings being presented in each minute. The task was scored for percentage of target strings correctly detected, average reaction time for correct detections (msec), and number of incorrect responses (false alarms).

Fatigue

Participants were asked to subjectively rate how mentally fatiguing they found the cognitive tasks. The visual analogue scales were displayed electronically at the end of every set of tasks. The scale was anchored 'Not at all' and 'extremely', with higher scores representing more mental fatigue.

Near infrared spectroscopy

Near infrared spectroscopy (NIRS) utilises the optical absorption properties of oxygenated haemoglobin and deoxygenated haemoglobin after the introduction of near-infrared light through the intact skull for the purpose of indirectly measuring of neuronal activity [38]. When assessed by NIRS, an increase in blood flow in the surface layers of the cortex during localised neural activity is seen as an increase in the total concentration of oxyhaemoglobin and comparative decrease in deoxyhaemoglobin [39], with both variables corresponding strongly with the fMRI BOLD signal [39,40]. Several peer reviewed intervention studies have utilised NIRS to assess the effects of nutritional interventions upon cerebral blood flow [41,42]. In the current study, cerebral blood flow was measured using the method reported by Kennedy et al. [29], a method which has previously been shown to be sensitive to nutritional interventions with similar goals as the current study [29–31]. Whereby, a 12-channel Oxymon system (Artinis Medical Systems BV, Zetten, Netherlands) was used to measure relative changes in absorption of near-infrared light at a time resolution of 10 Hz. The system emitted two wavelengths of light (765 and 855 nm). The differential path length factor was adjusted according to the age of the participant. A simple 2-emitter/optode pair configuration was used in the current study with emitter/optode pairs positioned over the left and right frontal cortex by using a standard optode holder headband, which separated the emitter/optode pairs by 4 cm. Each pair, therefore, collected data from an area of the prefrontal cortex that included the areas corresponding to the International 10–20 system Fp1 and Fp2 EEG positions. Proprietorial software was used to calculate relative concentration changes in oxyhaemoglobin, deoxyhaemoglobin, and total-haemoglobin by means of a modified Beer–Lambert law [43]. The NIRS data output was time stamped at the start of each event segment (baseline, absorption and each cognitive task) to ensure that data corresponded to the relevant epoch. Events which could impact data (excessive head movements, head scratching, sneezing etc.) were also recorded for the purpose of data cleaning.

Procedures

Each participant was required to attend one screening session and two study days which were conducted at least seven days apart to ensure a sufficient wash out period between conditions. There was no standardisation of food intake between visits, participants were however asked to consume no purple coloured berries or alcohol for 24 hours before each study day. They were also asked to refrain from physical activity and caffeine consumption for 12 hours before each visit. Cognitive testing took place in a laboratory where participants were individually tested in an environment isolated from noise and other physiological distractions. On arrival at their first session, participants were randomly allocated to a treatment regime using a Latin square design that counterbalanced the order of treatments across the two active days of the study. On all testing days participants arrived in the laboratory at 8 am (after a 12 hour overnight fast) and were firstly fitted with a NIRS headband. After a five-minute seated resting period, NIRS recording began and continued throughout the entire session. Participants then completed one set of the cognitive demand battery which was used as the baseline cognitive measure. The participant then rested for 10 minutes, this was used as the pre-dose resting baseline measurement for NIRS paradigms. The participant was then supplemented with either the active treatment or sugar and flavour matched control (depending on randomisation). After a one hour resting absorption period, during which the participant was required to sit and watch an episode of Grand Designs, Channel4 which was randomly allocated to ensure participants had a novel show for each occasion, the participant completed a modified version of the cognitive demand battery. A one hour absorption period was chosen to coincide the cognitive assessment with the peak appearance of anthocyanins in blood [44,45] and inhibition of monoamine oxidase A and B [18]. The running order of the testing session can be seen in Figure 1.

Statistical analysis

Fatigue, cognitive scores and NIRS measures were analysed as ‘change from baseline’ using the SPSS 18 statistics package. Baseline differences were calculated for all mood and cognitive measures using a one-way (treatment) ANOVA.

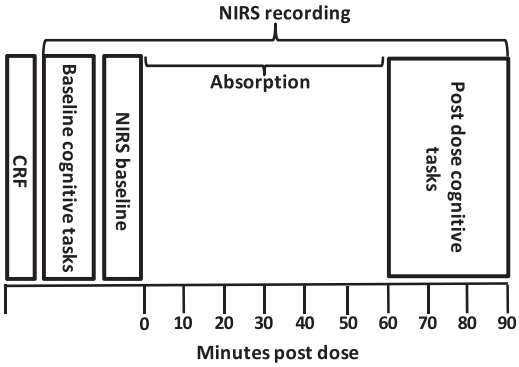

Figure 1. Test session running order (minutes). CRF = case report form, NIRS = near infrared spectroscopy.

Haemodynamic outcomes were assessed using 12, five-minute, epochs during the 60-minute absorption and for the full duration of each cognitive task (2 minutes for serial subtraction tasks and five minutes for the RVIP task) during the cognitive demand battery (9 epochs). The baseline measure was calculated using the final two minutes of the 10-minute resting baseline period immediately prior to ingestion of the study drinks.

Cognitive measures and fatigue ratings were analysed with repeated measures ANOVAs (General linear model) by treatment [control and 500 mg] and completion [1–3]. Repeated measures ANOVAs (General linear model) by treatment [control and 500 mg], epoch [1–21. Epoch 1–12 for the resting period and 13–21 for the cognitive tasks] and hemisphere [left and right] were conducted on the entire session for haemodynamic outcomes. Where no hemispheric differences were observed, data for the two hemispheres were combined and this factor (hemisphere) was omitted from the analyses. Mauchly`s test of sphericity was used to assess equality of the variances of the differences between factors. Where sphericity had been violated, Huynh-Feldt corrections for non-sphericity were implemented.

Pairwise comparisons with Bonferroni corrections for multiple comparisons were conducted on all outcomes with a P value <0.05 from the initial mixed model analysis to ascertain any differences between treatments for the whole session and at specific epochs.

Results

Twenty healthy adults completed all study visits (6 male and 14 female). The mean age of the participant's was 22.3 ± 3.6 years, with a mean body mass index of 23.14 ± 2.66 kg/m^2. A consort diagram of participant flow can be found in Figure 2.

Cognitive outcomes

There were no significant differences found between treatments on any measures at baseline. There were no significant differences found between treatments for any of the cognitive outcomes or self-reported fatigue. Unadjusted baseline and post dose data for visual analogue fatigue and all cognitive and tasks can be found in Table 3.

The data show that fatigue incrementally increased across both conditions. This change is significant F = 5.64 P = 0.005. When compared against norms, the data don't indicate any ceiling effects in performance.

NIRS outcomes

Tables of data for all NIRS outcomes can be found in the online supplementary data Table 2.

Oxyhaemoglobin

The repeated measures ANOVA revealed a significant treatment*hemisphere interaction for oxyhaemoglobin [F(1,19) = 6.813, p = 0.018]. Pairwise comparisons showed an increase in oxyhaemoglobin in the left

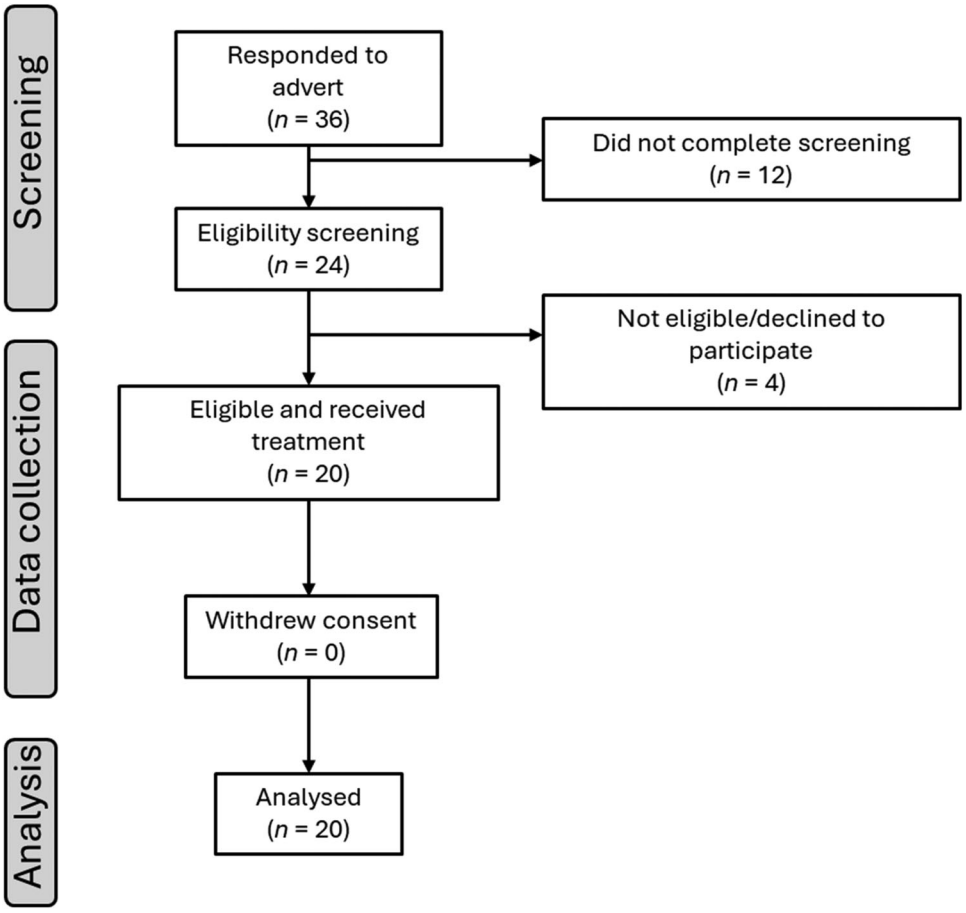

Figure 2. consort diagram.

hemisphere following consumption of the Blackadder juice when compared to control ($p = 0.019$), with no effect of treatment on the right hemisphere.

There was also a significant treatment*hemisphere*epoch interaction [$F(1.88,33.83) = 7.70$, $p = 0.002$]. Pairwise comparisons revealed an increase in oxyhaemoglobin in the left hemisphere after consumption of the Blackadder juice drink when compared to control at the following epochs; 5 minutes ($p = 0.014$), serial 3s repetition 1 ($p = 0.008$), serial 7s repetition 1 ($p = 0.023$), RVIP repetition 1 ($p = 0.023$), serial 3s

Table 3. Unadjusted baseline and post dose data for cognitive tasks and visual analogue fatigue.

		Baseline		Post dose 1		Post dose 2		Post dose 3	
Task	Treat	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Serial Subtraction 3s – Correct Responses	Con	44.20	11.43	44.65	11.82	45.50	11.96	44.90	10.40
	BC	42.85	17.16	44.05	16.72	43.75	15.70	42.05	13.92
Serial Subtraction 3s – Error Responses	Con	1.95	2.74	2.25	3.34	2.70	3.53	3.40	4.11
	BC	2.80	3.89	2.05	3.02	3.55	3.38	4.10	3.60
Serial Subtraction 7s – Correct Responses	Con	24.25	10.96	27.05	27.05	27.05	27.05	26.80	26.80
	BC	25.25	12.08	28.00	11.91	28.30	10.88	28.00	11.74
Serial Subtraction 7s – Error Responses	Con	2.95	2.95	2.95	2.95	3.05	3.05	3.85	3.85
	BC	2.80	2.86	2.75	2.65	3.30	2.94	2.75	2.75
RVIP – % Correct	Con	53.50	22.89	53.25	23.55	52.00	21.97	53.63	25.91
	BC	56.63	21.33	56.25	22.75	51.63	23.89	52.63	23.01
RVIP – Correct RT	Con	482.88	59.83	483.24	57.99	478.14	49.35	477.06	64.43
	BC	482.74	59.60	479.83	51.76	497.88	88.73	447.42	115.29
RVIP – False Alarms	Con	0.85	1.23	0.70	0.92	1.15	1.50	1.00	1.41
	BC	0.90	1.59	1.10	1.25	0.65	1.18	1.35	1.46
VAS Fatigue	Con	28.60	17.42	44.60	26.88	50.70	29.98	54.40	31.30
	BC	23.75	17.85	34.90	26.94	43.00	29.63	47.10	30.98

BC = Blackcurrant; Con = Control; RVIP = Rapid Visual Information Processing.

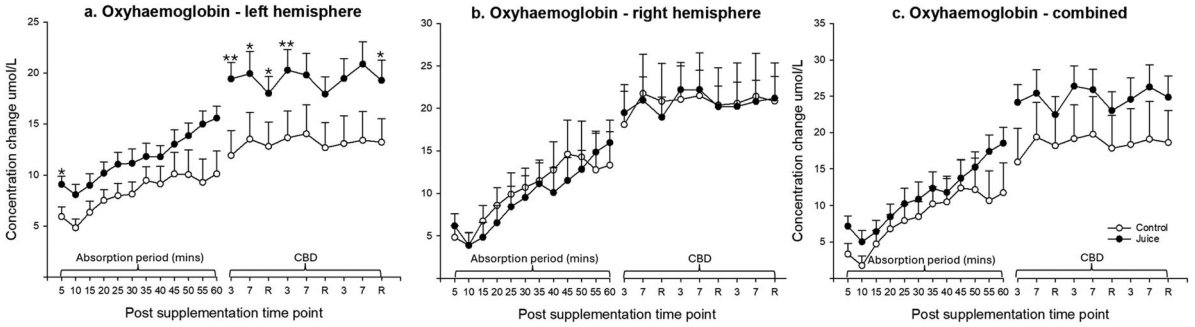

Figure 3. Change from baseline oxyhaemoglobin throughout the 60 min absorption period and cognitive demand battery (CDB) (a) the left hemisphere, (b) the right hemisphere and (c) left and right hemispheres combined. Significant differences are indicated on the graph (*$p < 0.05$, **$p < 0.01$).

repetition 2 ($p = 0.008$),, RVIP repetition 2 ($p = 0.009$), and RVIP repetition 3 ($p = 0.014$) with no interpretable effect of treatment on the right hemisphere. A graphical representation of all NIRS oxyhaemoglobin outcomes can be seen in Figure 3.

Deoxyhaemoglobin

The ANOVA revealed a significant effect of treatment on deoxyhaemoglobin [$F(1,19) = 5.70$, $p = 0.027$]. This was due to a decrease in deoxyhaemoglobin after consumption of the Blackadder juice when compared to control.

The ANOVA also revealed a significant treatment*epoch interaction for the entire session [$F(20,380) = 2.73$, $p = 0.001$]. Pairwise analysis revealed a decrease in deoxyhaemoglobin after the Blackadder juice treatment when compared to control at the 5 min ($p = 0.01$), 50 min ($p = 0.018$), 55 min ($p = 0.01$), 60 min ($p = 0.009$), serial 3s repetition 1 ($p = 0.013$) and serial 7s repetition 3 ($p = 0.017$) epochs. Trends towards the same pattern of modulation were seen at the 45 min ($p = 0.06$), serial 7s repetition 1 ($p = 0.088$), RVIP repetition 1 ($p = 0.05$), serial 3s repetition 2 ($p = 0.068$), serial 7s repetition 2 ($p = 0.069$), RVIP repetition 2 ($p = 0.076$) and serial 3s repetition 3 ($p = 0.053$) epochs. A graphical representation of all NIRS deoxyhaemoglobin outcomes can be seen in Figure 4.

Total haemoglobin

There was a significant treatment*hemisphere interaction for total haemoglobin [$F(1,18) = 7.06$, $p = 0.011$]. There were no significant differences between treatments after corrections for multiple comparisons.

The ANOVA also revealed a significant treatment*hemisphere*epoch interaction for total haemoglobin [$F(3.763,364.2) = 3.161$, $p = 0.021$]. Pairwise comparisons revealed an increase in total haemoglobin in the left hemisphere when compared to control at the; 5 min ($p = 0.021$) 10 min ($p = 0.027$).

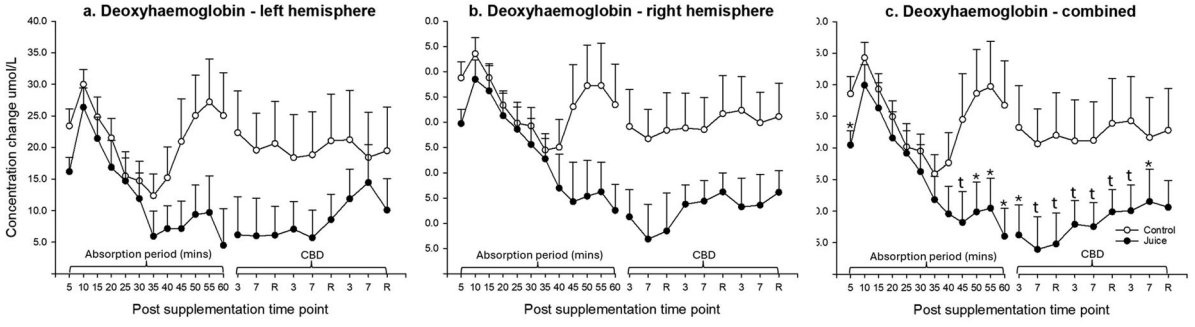

Figure 4. Change from baseline deoxyhaemoglobin throughout the 60 min absorption period and cognitive demand battery (CDB) for (a) the left and right hemisphere, (b) the right hemisphere and (c) left and right hemispheres combined. Significant differences are indicated on the graph (*$p < 0.05$, t $p < 0.1$).

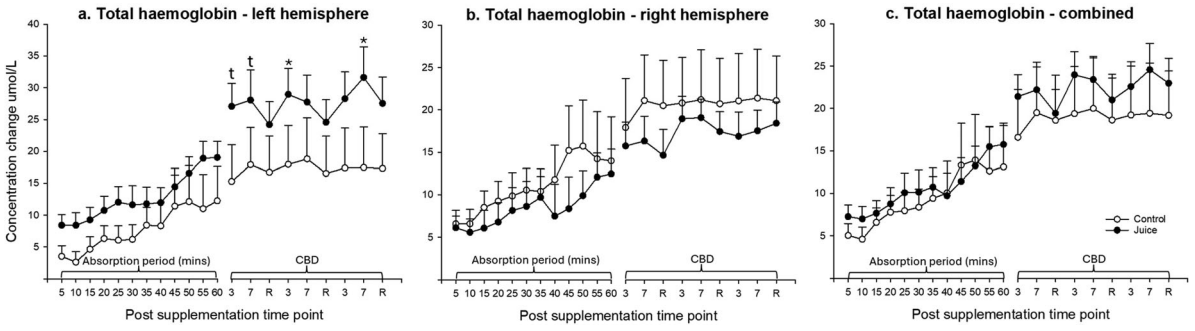

Figure 5. Change from baseline total haemoglobin throughout the 60 min absorption period and cognitive demand battery (CDB) for (a) the left hemisphere, (b) the right hemisphere and (c) left and right hemisphere combined. Significant differences are indicated on the graph ($p < 0.1$, *$p < 0.05$, **$p < 0.01$).

A trend towards the same pattern of modulation was seen at the 50 min epoch ($p = 0.052$), Serial 3s repetition 1 ($P = 0.096$) Serial 7s repetition 1 ($P = 0.075$) and serial 7s repetition 3. A graphical representation of all NIRS total haemoglobin outcomes can be seen in Figure 5.

Discussion and conclusion

The aim of the current study was to assess the impact of the MAO inhibiting Blackadder blackcurrant juice extract upon cognition and shallow pre-frontal cortical haemodynamics. The study focused upon two aspects, acute pre-frontal cortical haemodynamics under cognitive demand and pre-frontal cortical haemodynamics at rest. The overall pattern of task-related changes in local haemoglobin concentrations independent of intervention was as expected [22,30], with increases in oxyhaemoglobin and decreases in deoxyhaemoglobin during cognitive task performance and, therefore, increases in regional cerebral blood flow.

When compared to placebo, the consumption of the Blackadder juice extract resulted in significant modulations of pre-frontal cortex haemoglobin concentrations during resting absorption and cognitive task performance, with apparent hemispheric differences. An increase in oxyhaemoglobin and total haemoglobin in the left hemisphere, but not the right, was seen after consumption of the blackcurrant drink when compared to control, with significant increases being found throughout the cognitive demand period with no effect of task type. In relation to concentration changes in deoxyhaemoglobin, supplementation of the Blackadder blackcurrant extract caused a significant or near to significant trend reduction in overall deoxyhaemoglobin (left and right hemispheres combined), beginning during the resting absorption period, 45 minutes post supplementation of the blackcurrant juice. This reduction continued throughout the remaining absorption period and throughout the cognitive testing period, again with no effect of task type.

With regards to intervention-related modifications in concentrations of total and oxygenated haemoglobin, increases have been observed during cognitive demand after oral supplementation of cocoa flavanols [24], resveratrol [22,29], anti-depressants [46] and vinpocetine [47]; however, with no hemispheric differences seen. As increased oxyhaemoglobin and total haemoglobin have been linked to increased neural activity during cognitive demand in healthy young adults when measured by NIRS [48], the rise in total haemoglobin in response to post-dose tasks in the current study could demonstrate neurovascular coupling, which is further up-regulated in the left hemisphere after consumption of the blackcurrant juice. As the tasks in the present study have been shown to increase activity in the pre-frontal cortex [49] and the pre-frontal left hemisphere [50], the hemispheric differences found in the present study could be an effect of the study intervention amplifying a natural difference in hemispheric activity in response to cognitive performance. However, it must be noted that there is no observable difference in hemispheric activity shown in the current study after consumption of the control intervention. When assessed via PET without a nutritional intervention, the RVIP task has been shown to elicit increases in regional cerebral blood flow bilaterally in the inferior frontal gyri, parietal cortex and fusiform gyrus, as well as lateralised right-sided activation in superior frontal gyrus [49]. When RVIP was compared to a simplified version of the task

with the working memory element removed, the right frontal activations were no longer apparent. The authors consider these findings consistent with the existence of a right fronto-parietal network for sustained attention, and a left fronto-parietal network for working memory. Therefore, the increase in left hemisphere regional cerebral blood flow following blackcurrant supplementation in the current study, could be indicative of increased neuronal activation in brain areas associated with working memory. The mechanism is not known and it is not thought that it is a direct action of polyphenols on the brain but could be an effect of the inhibition of MOA-A and B via sarmenrosin [19] and subsequent influence upon the monoamine axis [18]. These mechanisms need further investigation.

Given the increase in oxygenated haemoglobin in the left hemisphere following supplementation of the Blackadder extract, a relative decrease in deoxygenated haemoglobin is expected. This is due to the rate of utilisation of oxygen being slower than the rate at which it is provided. However, the effects on deoxygenated haemoglobin do not show the lateralisation observed with oxygenated haemoglobin, which, coupled with the time of onset of effects suggests that another mechanism is involved in the effects on deoxyhaemoglobin. The significant effects upon deoxyhaemoglobin seem to be brought about by a divergence in effects at around 35 minutes post-consumption. Prior to this, both treatments have followed a similar pattern of increase at 10 minutes post-consumption followed by a decline up until 35 minutes. At this point, deoxyhaemoglobin levels begin to rise back up in the control group until they reach a level similar to that observed at baseline. Conversely, values in the Blackadder juice group continue to fall before levelling off for the remainder of the session. As both the active and control drink followed the same pattern of modulation until 35 minutes post-dose, it would suggest that the effects are caused by a common denominator, however the mechanisms behind this are unknown. It must also be noted that a significant increase in regional cerebral blood flow, as indexed by total haemoglobin, was seen at the ten-minute epoch, post-consumption of the blackcurrant intervention as compared to control. It seems unlikely that this early effect is attributable to modulations of biological mechanisms by phenolic compounds within the study drinks, with a more plausible explanation being that it is related to subtle differences between sensory properties of the Blackadder juice extract and the control drink. fMRI clearly shows that a number of factors related to the sensory properties of a food or drink can directly modulate frontal cortex activity, including differing tastes [51] and flavours [52].

Substantiated evidence of underlying mechanisms driving changes in haemodynamics after administration of a nutritional intervention are yet to be fully understood. Although anthocyanins have been found in the brains of rats after oral ingestion [53,54], bioavailability of anthocyanin compounds is extremely low and, therefore, their direct effect upon the site of action is doubtful. However, given that nitric oxide synthesis plays a major role in the modulation of localised blood flow in the neural tissue of animal models [55], the pattern of increased oxyhaemoglobin and total haemoglobin in the left hemisphere during cognitive tasks only, could indicate intervention-dependent, nitric oxide synthesis driven neurovascular coupling in the frontal cortex. This neurovascular coupling involves the coordinated interaction of neurons, glia, and vascular cells and is, therefore, a key regulator in the maintenance of normal blood flow in the cerebral cortex during brain activity. It must be noted that blood flow was only measured in a very small and superficial part of the frontal cortex, therefore, the effects cannot be generalised to other regions of the brain or frontal cortex.

MAO inhibitors act upon neurotransmitters such as dopamine and serotonin which affect regional cerebral blood flow [56], and are mediators of nitric oxide in animal models of hypertension [57], therefore, the impact of MAO inhibition by the Blackadder blackcurrant extract cannot be overlooked as a possible mediator of the haemodynamic changes seen in the current study. Dopamine, which is deaminated by MAO-B, has been established as a modulator of neuronal blood flow [58] and is theorised to be implicated in diminished blood flow in pathological diseases such as Parkinson's disease [59]. Therefore, increased CNS levels of dopamine modulated by inhibition of central MAO-B as shown in our previous papers after the consumption of a blackcurrant drink [16,18], could drive increases in neuronal activity and, therefore, have modulated haemodynamics in the current study. Reductions in levels of deoxyhaemoglobin coincide with the appearance of berry anthocyanins in blood plasma which reach maximal concentrations at ~1-1.5 hour post consumption [44,45]. Pharmacokinetics of anthocyanins pre-one hour post oral ingestion have not been published; however, it seems reasonable to assume that anthocyanins would be present in blood plasma 45 minutes post ingestion.

Levels of vitamins and minerals were not assessed in the blackcurrant juice under investigation in this study and were therefore not matched between the active and control drinks. Blackcurrants contain a range of vitamins such as niacin (0.3 mg/100 g), riboflavin (0.05 mg/100 g)., vitamin B6 (0.06 mg/100 g)., vitamin E (1 mg/100 g) and ascorbic acid (181 mg/100 g) [60]. Previous studies have shown that acute supplementation with multivitamins can influence CBF during cognitive assessments [61]. However, other than for ascorbic acid, doses supplemented in the Kennedy et al. article were much greater than can be expected after consumption of blackcurrant juice. The interaction between vitamins and minerals and the changes in CBF in the current study can, however, not be ruled out. Similarly, post prandial blood glucose concentrations were not assessed in the current study. The cerebral metabolic rate of oxygen, as measured by fMRI, has been shown to be reduced after supplementation with 50 g of glucose [62]. Our previous study [18] showed that peak post prandial glucose concentrations are reduced by ~0.5 mmol/L and delayed by ~15 minutes after consuming blackcurrants compared to a sugar match control. Therefore, there is a possibility that the effects seen within this study are due to a difference in post prandial glucose availability, but it is unlikely that the dose of <4 g of glucose would be responsible for the changes in NIRS outcomes.

It was not in the remit of this study to assess the habitual diet of the participants. Previous research has shown that lower habitual flavonoid consumers benefit from flavanol consumption in terms of improvements in cognitive performance [63]. Future research in the area may benefit from assessing how habitual diet and chronic polyphenol intake may influence physiological changes or cognitive performance alterations after the consumption of blackcurrants.

The study treatment showed no effect upon cognitive task performance. Although previously shown to be sensitive to doses of 520 and 994 mg of cocoa flavonoids [37], the tasks employed here were chosen on the basis that they have previously been shown to activate the prefrontal cortex [64,65] and generate a haemodynamic response in the frontal cortex [26,30,31], rather than because they have been shown to be sensitive to polyphenol supplementation. In relation to dosage, the heterogeneity in study protocols and polyphenols under investigation impact the ability to make clear dosage recommendations for the acute effects of polyphenols upon cognitive function. A recent meta analysis [66] outlines that a polyphenol dose of at least 250 mg (ranging between 250 mg – 500 mg dependant on intervention) is needed to acutely improve working memory tasks such as serial subtractions and doses of >300 mg are needed to see acute improvements in reaction time based tasks. The 500 mg dose of polyphenols used in this study is consistent with previous research demonstrating acute cognitive benefits in adults, particularly on tasks assessing attention and working memory, such as Serial Subtractions and RVIP (520 mg of cocoa polyphenols) [37], working memory (320 ml of grape polyphenols) [67] and reaction times (500 mg blackcurrant) [17]. These findings along with our other previous work on blackcurrants [16] indicates that a dose of 500 mg of blackcurrant polyphenols should acutely enhance cognitive performance, particularly in tasks requiring sustained attention, working memory, and executive function. It may be the case that the tasks are demanding enough to activate the frontal cortex but not demanding enough to show differences in cognitive performance between treatments. A previous study showed that the task difficulty influences the ability to detect changes in cognitive performance between treatments after supplementation of cocoa flavanols or control [27] our previous study. Future paradigms should consider assessing task difficulty alongside tasks known to influence the prefrontal cortex. It should also be acknowledged that the samples size for the current study was based on the primary outcome, which was CBF. Since effects of flavonoid rich interventions have been seen on RVIP in young adults [16] and serial subtractions in older adults [68], the study may have been underpowered to detect effects on cognition.

Results from the current study outline an increased NIRS response in brain regions responsible for task performance after supplementation with the Blackadder blackcurrant extract when compared to control. This is not coupled with an increase in cognitive performance in measured paradigms. To attempt to assess if blood flow changes are general, or solely an artefact of an amplification of neurovascular coupling in a specific brain region following the blackcurrant intervention, a suggestion for future research would be to assess cognitive tasks which are not dependent on frontal cortex activity alongside tasks which are. Furthermore, the cohort used in the present study had no apparent issues pertaining to cerebral blood flow. The tight regulation of blood flow in the brain could mean that sufficient blood flow already exists for maximal cognitive performance and, therefore, increasing blood flow above this threshold does not have any acute benefits upon cognitive performance. The use of a cohort in which cerebral blood flow has potentially

reduced, could highlight differential cognitive results. In light of findings by Decroix et al. [69] and Gratton et al. [27] where modulations on cognitive improvements were seen after consumption of cocoa flavonoids during hypoxic conditions, hypoxia could be used in future blackcurrant studies of young adults to understand if cognitive improvements can be seen when oxygen delivery is not optimal.

Results from this trial outline the ability of the Blackadder blackcurrant juice extract to increase cerebral blood flow during cognitive activity in healthy young adults. The effects of the Blackadder juice extract in addition to other types of blackcurrant extracts upon acute and chronic brain function and blood flow deserves further investigation.

Disclosure statement

Dr Arjan Scheepens was an employee of Plant and Food Research Ltd. during the time when the study was conducted.

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