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ORIGINAL INVESTIGATION

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Cognitive and physiological effects of an "energy drink": an evaluation of the whole drink and of glucose, caffeine and herbal flavouring fractions

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Abstract *Rationale:* Both glucose and caffeine can improve aspects of cognitive performance and, in the case of caffeine, mood. There are few studies investigating the effects of the two substances in combination. *Objectives:* We assessed the mood, cognitive and physiological effects of a soft drink containing caffeine and glucose as well as flavouring levels of herbal extracts. The effects of different drink fractions were also evaluated. *Methods:* Using a randomised, double-blind, balanced, five-way crossover design, 20 participants who were overnight fasted and caffeine-deprived received 250 ml drinks containing 37.5 g glucose; 75 mg caffeine; ginseng and ginkgo biloba at flavouring levels; a whole drink (containing all these substances) or a placebo (vehicle). Participants were assessed in each drink condition, separated by a 7-day wash-out period. Cognitive, psychomotor and mood assessment took place immediately prior to the drink then 30 min thereafter. The primary outcome measures included five aspects of cognitive performance from the Cognitive Drug Research assessment battery. Mood, heart rate and blood glucose levels were also monitored. *Results:* Compared with placebo, the whole drink resulted in significantly improved performance on "secondary memory" and "speed of attention" factors. There were no other cognitive or mood effects. *Conclusions:* This pattern of results would not be predicted from the effects of glucose and caffeine in isolation, either as seen here or from the literature addressing the effects of the substances in isolation. These data suggest that there is some degree of synergy between the cognition-modulating effects of glucose and caffeine which merits further investigation.

Keywords Glucose · Caffeine · Ginseng · Ginkgo biloba · Cognition · Mood · Heart rate · Blood glucose

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Introduction

There is a wealth of research demonstrating that the ingestion of either glucose or caffeine can benefit cognitive performance. The recent widespread growth in the use of "energy drinks" containing both substances has not been matched by research directed at determining the behavioural effects of the substances in combination, despite claims by manufacturers that such drinks benefit mental function. Even less work has examined the potential cognitive effects of other substances present in such drinks at presumed sub-pharmacological levels.

It is well documented that aspects of psychological performance can be enhanced following the administration of a drink containing 25–50 g of glucose. Cognitive tasks affected include those assessing memory (e.g. Foster et al. 1998; Sünram-Lea et al. 2002), reaction times (Owens and Benton 1994), rapid visual information processing (Benton et al. 1994; Donohoe and Benton 1999), the Stroop paradigm (Benton et al. 1994), Porteus maze and Block Design tasks (Donohoe and Benton 1999), the Brown–Peterson working memory task (Martin and Benton 1999), driving simulator performance (Keul et al. 1982), kinaesthetic memory (Scholey and Fowles 2002), face recognition (Metzer 2000), and serial subtraction mental arithmetic (Kennedy and Scholey 2000; Scholey et al. 2001). It has been suggested that glucose may differentially target verbal declarative memory despite a growing number of studies which have failed to find any direct effect of glucose on tasks assessing this domain (Azari 1991; Scholey et al. 2001; Ford et al. 2002). An alternative suggestion is that glucose preferentially affects tasks where the processing load is relatively high (Korol and Gold 1998; Kennedy and Scholey 2000; Scholey et al. 2001), a proposal which is supported to some degree by the finding that glucose enhancement of memory was observed only when participants co-performed a secondary task (Sünram-Lea et al. 2002). Nevertheless, it is possible that the addition of a second psychopharmacologically active substance such as caffeine to a glucose drink

might more successfully affect memory processes even under relatively non-demanding task conditions.

The literature pertaining to caffeine has reported a number of beneficial psychological and performance effects. Some studies are confounded to a degree by the use of caffeine doses in excess of those consumed in everyday circumstances. However, when realistic doses have been used caffeine improves performance by reducing reaction times and improving attentional performance (for reviews, see Warburton 1995; Koelega 1998; Smith 2000, 2002). Enhancement can most parsimoniously be described as being seen across psychomotor and vigilance tasks, particularly when responses are sustained over time. Caffeine is also consistently associated with modulation of mood, most notably increasing alertness and reducing fatigue (Smith 2002).

A series of experiments have assessed the cognitive and mood effects of an inferred glucose load from a meal in cohorts who also consumed either caffeinated or decaffeinated coffee. Whilst these studies have tended to confirm an enhancement of cognitive performance and mood following caffeine (e.g. Smith et al. 1990, 1994a,b, 1999), the behavioural effects of a meal have been shown to vary with the time of day. In general, breakfast has been shown to enhance cognitive performance (e.g. Smith et al. 1994a, 1999), whilst day-time and evening meals have been shown to impede some aspects of cognitive performance (e.g. Smith and Miles 1986; Smith et al. 1990, 1994b).

A number of studies have also assessed the behavioural effects of "energy" drinks containing both glucose and caffeine, along with other potentially active agents. Several have assessed the effects of a commercial drink containing caffeine, taurine, glucoronolactone, and vitamins amongst its ingredients. These studies have identified improvements in aerobic and anaerobic cycling performance (Alford et al. 2000), performance of attentional and/or reaction time tasks (Alford et al. 2000; Warburton et al. 2001), afternoon driving performance (Reyner and Horne 2002) and various indices of alertness (Alford et al. 2000; Warburton et al. 2001; Reyner and Horne 2002). Similarly, Seidl et al. (2000) examined the effects of capsules containing amounts of caffeine, taurine and glucoronolactone equivalent to one drink. They found that the decrements in P300 latency and reaction times, attention task performance and alertness associated with night time testing, were ameliorated in the active condition in comparison to an inert placebo.

Smit and Rogers (2002) compared the behavioural effects of two tailor-made energy drinks with a still water condition and a "no-treatment" condition. Both energy drinks provided the same number of calories from glucose (Rogers, personal communication), and contained 75 mg caffeine (in the case of one drink, partly derived from a guarana extract). In comparison to water, no effects of the active treatments were found for either memory or rapid visual information processing, but simple reaction time and self-ratings of "energetic-arousal" were significantly improved by both drinks.

Whilst these studies suggest the possibility that glucose and caffeine containing "energy drinks" might enhance mood and cognitive performance, no study has adequately addressed the relative contributions of the drinks main constituents. The single exception here is Warburton et al.'s (2001) study which reported two separate studies comparing a whole drink (containing caffeine, taurine and glucoronolactone) to a non-glucose drink and to a glucose-containing drink, respectively (other details of the placebos are not provided). In both studies the active drink improved accuracy and speed of rapid information processing, logical reasoning speed and enhanced three of the same mood items (alert, clearheaded and attentive) from the Bond and Lader (1974) Visual Analogue Scales suggesting a robust behavioural effect of the energy drink. Indeed inspection of Tables 1 and 2 reveals that many mood effects were remarkably consistent across the two studies (Warburton et al. 2001, p. 325).

In addition to the behavioural modulation described above, both caffeine and glucose have peripheral effects. As well as its obvious hyperglycaemic effects, glucose ingestion is associated with heart rate acceleration (Kennedy and Scholey 2000; Ford et al. 2002). On the other hand, the physiological effects of caffeine administration include heart rate deceleration (Passmore et al. 1987; Pincomb et al. 1991; Quinlan et al. 2000), although other authors have found no effects (Quinlan et al. 1997; Lane and Phillips-Bute 1998). The effects on heart rate of caffeine and glucose in combination are not known.

Given that caffeine is often consumed with a source of glucose, either from accompanying food, or directly in the recently developed "energy drinks" and confections, it seems timely to address the relative contributions that glucose and caffeine might make to enhancement of cognitive performance, mood and physiology. The current double-blind, placebo-controlled, balanced cross-over study therefore compared the effects of a non-calorific placebo drink (vehicle) with: a complete "energy drink" (vehicle, glucose, caffeine including from guarana, flavouring levels of herbs); the glucose fraction (vehicle plus glucose); the caffeine fraction (vehicle plus caffeine/guarana); and the flavouring fraction (vehicle plus herbal flavourings).

The cognitive effects of these drinks were examined using a tailored version of the Cognitive Drug Research (CDR Ltd) computerised assessment battery and computerised Serial Subtraction mental arithmetic tasks. These have been shown to be sensitive to the effects of numerous interventions including those resulting from herbal extracts, glucose and caffeine (Kennedy and Scholey 2000; Kennedy et al. 2000, 2001a,b, 2002a,b; Scholey et al. 2001; Scholey and Kennedy 2002; Haskell et al., unpublished data). Any effects of the drinks on psychomotor speed and mood were also assessed. Physiological measures (heart rate and blood glucose levels) were co-monitored.

Materials and methods

Participants

Fourteen female and six male undergraduate volunteers (mean age 21.1 years, age range 18–32 years) took part in the study which was approved by the Northumbria University Division of Psychology Ethics Committee. Prior to participation each volunteer signed an informed consent form and completed a medical health questionnaire. All participants reported that they were in good health, and were taking no illicit social drugs. Additionally, they were free of any "over the counter" or prescribed medications, with the exception, for some female volunteers, of the contraceptive pill. Smokers were excluded from the study. All participants were overnight fasted and abstained from caffeine-containing products on the mornings of the study, and alcohol for a minimum of 12 h prior to the first testing session of study days.

Physiological measurements

Blood glucose levels

Blood glucose levels were determined using a MediSense Exac-tech Blood Glucose Sensor and disposable MediSense Blood Glucose Test Strips (MediSense Britain Ltd, Birmingham, UK). The high accuracy and consistency of MediSense blood glucose sensors has previously been established (e.g. Mathews et al. 1987).

Blood samples were taken using Owen Mumford "Unistik 2" single use capillary blood sampling devices (Owen Mumford Ltd, Oxford, UK). Alcohol-soaked Medi-swabs were used for pre-sampling sterilisation (Smith and Nephew, UK).

Heart rate

Heart rates were measured using a N100-P hand-held pulse oximeter (Nellcor Puritan Bennet, Coventry, UK) according to the manufacturer's instructions. Average heart rates were calculated over 60-s epochs.

Assessment of mood

Bond–Lader visual analogue scales

Bond–Lader visual analogue scales (Bond and Lader 1974), were combined as recommended by the authors to form three mood factors: "alert", "calm" and "content".

Profile of Mood States

The Profile of Mood States (POMS) questionnaire (Loor and McNair 1980) consists of 72 items measuring six bipolar dimensions of mood; "agreeable–hostile", "clearheaded–confused", "composed–anxious", "confident–unsure", "energetic–tired", and "elated–depressed". Each of these measures generates a score of between −18 and +18 with positive scores indicating a more positive mood on each dimension.

Cognitive assessment

Digit Symbol Substitution Task

The Digit Symbol Substitution Task (DSST) (Weschler 1958) is a standardised paper-and-pencil test of psychomotor speed (errors are rare), where each number from 1 to 9 has a corresponding symbol displayed in a key at the top of the page. Participants are required to enter the correct symbol beneath each given digit in an array of digits as quickly as possible. The number of correct symbols generated in 90 s was recorded.

Cognitive Drug Research computerised assessment battery

The Cognitive Drug Research (CDR) computerised assessment battery has been used in hundreds of European and North American drug trials, and has been shown to be sensitive to acute cognitive improvements as well as impairments with a wide variety of substances (e.g. Moss et al. 1998; Scholey et al. 1999; Kennedy et al. 2002a, 2003).

The current study utilised the tailored version of the CDR battery, and the cognitive factors derived by factor analysis from it that has previously been found to be sensitive to modulation of cognitive function as a consequence of acute and chronic ingestion of a number of herbal extracts (Kennedy et al. 2000, 2001a,b, 2002a,b, 2003).

The selection of computer controlled tasks from the system was administered with parallel forms of the tests being presented at each testing session. Presentation was via desktop computers with high resolution VGA colour monitors, and, with the exception of written word recall tests, all responses were recorded via two-button (YES/NO) response boxes. The entire selection of tasks took approximately 20 min.

Tests were administered in the following order:

Word presentation Fifteen words, matched for frequency and concreteness, were presented in sequence on the monitor for the participant to remember. Stimulus duration was 1 s, as was the inter-stimulus interval.

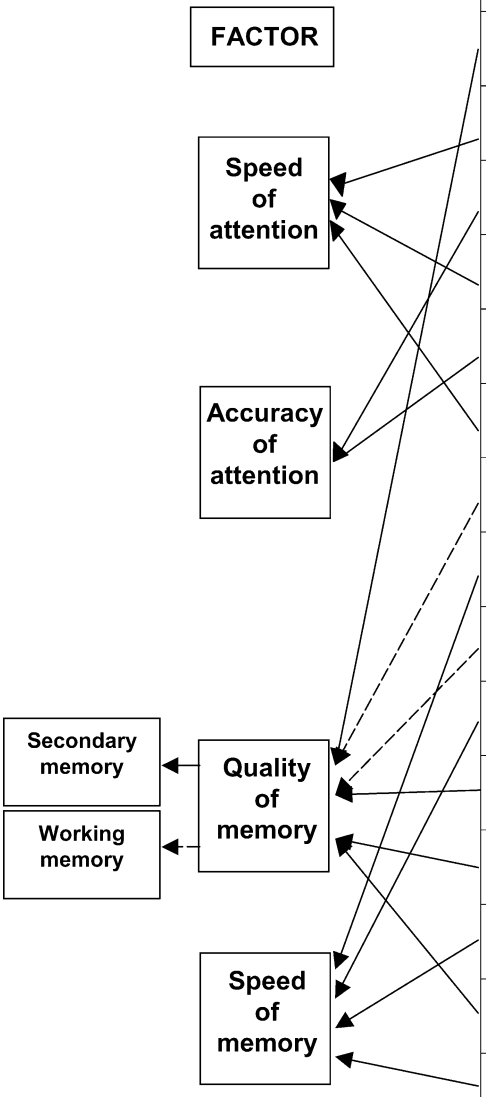
Immediate word recall The participant was allowed 60 s to write down as many of the words as possible. The task was scored as number of words produced, minus errors and intrusions and the resulting score was converted into a percentage.

Picture presentation A series of 20 photographic images of everyday objects and scenes were presented on the monitor at the rate of one every 3 s, with a stimulus duration of 1 s, for the participant to remember.

Simple reaction time The participant was instructed to press the "YES" response button as quickly as possible every time the word "YES" was presented on the monitor. Fifty stimuli were presented with an inter-stimulus interval that varied randomly between 1 and 3.5 s. Reaction times were recorded in milliseconds.

Digit vigilance task A target digit was randomly selected and constantly displayed to the right of the monitor screen. A series of digits was presented in the centre of the screen at the rate of 80 per minute and the participant was required to press the "YES" button as quickly as possible every time the digit in the series matched the target digit. The task lasted 1 min and there were 15 stimulus-target matches. Task measures were accuracy (%), reaction time (ms) and number of false positives.

Choice reaction time Either the word "NO" or the word "YES" was presented on the monitor and the participant was required to press the corresponding button as quickly as possible. There were 50 trials, of which the stimulus word was chosen randomly with equal



Task	Condition	Pre-dose score (s.e.)		Change from baseline score (s.e.)	
Immediate Word Recall *(% accuracy)*	placebo	63.17	3.98	-9.67	3.79
	complete drink	57.50	4.79	1.83	2.88 *
	glucose	63.17	4.21	-5.67	4.29
	caffigur	55.83	4.62	-4.17	4.17
	herbs	61.50	4.57	-7.50	3.62
Simple Reaction time (msecs)	placebo	253.44	8.57	6.57	4.82
	complete drink	252.61	7.13	-2.90	6.77
	glucose	254.35	7.19	5.14	7.51
	caffigur	247.79	7.31	8.12	3.95
	herbs	250.35	8.49	9.06	6.20
Digit Vigilance Accuracy (%)	placebo	95.50	1.17	-0.50	1.42
	complete drink	96.33	0.87	0.67	0.79
	glucose	96.67	0.73	-1.67	1.25
	caffigur	95.50	0.95	1.67	1.34
	herbs	96.17	1.31	-3.00	2.18
Digit Vigilance Reaction time *(msecs)*	placebo	398.33	10.51	9.56	5.29
	complete drink	397.57	9.90	-3.79	5.98
	glucose	406.38	10.33	3.93	8.70
	caffigur	395.46	9.03	-3.68	5.89
	herbs	399.77	10.10	8.16	5.77
Choice reaction time accuracy (%)	placebo	94.30	0.91	-0.50	0.92
	complete drink	94.70	0.87	-0.50	0.84
	glucose	95.00	0.97	-2.50	0.83
	caffigur	94.00	1.00	1.70	0.70 †
	herbs	93.50	1.00	1.20	1.03
Choice reactionTime *(msecs)*	placebo	388.57	9.34	9.12	7.45
	complete drink	388.30	11.32	-5.37	7.30
	glucose	381.98	9.71	10.57	7.64
	caffigur	391.27	9.04	-8.40	7.12 †
	herbs	386.55	11.57	7.17	9.62
Spatial Memory (%>chance)	placebo	92.56	1.29	-6.13	5.15
	complete drink	92.81	1.56	-3.19	2.49
	glucose	91.44	2.58	-4.38	3.17
	caffigur	90.00	1.74	-4.19	4.73
	herbs	92.31	1.55	-2.69	2.17
Spatial memory Reaction time *(msecs)*	placebo	589.28	22.01	-18.97	14.12
	complete drink	600.73	35.32	-32.07	17.24
	glucose	597.27	37.05	-28.47	23.36
	caffigur	590.12	31.41	-31.63	34.01
	herbs	560.01	21.45	2.46	25.19
Numeric W'king Memory *(%>chance)*	placebo	90.67	1.50	-3.89	1.23
	complete drink	88.34	1.77	-0.67	1.45
	glucose	86.78	1.45	-0.44	2.38
	caffigur	89.00	1.88	0.33	2.26 †
	herbs	89.34	2.11	-1.00	1.41
Numeric W'king Memory Reaction Time *(msecs)*	placebo	574.69	26.03	-13.28	11.55
	complete drink	578.22	26.87	-43.99	16.78
	glucose	563.20	26.38	-22.18	11.52
	caffigur	556.58	21.22	9.58	24.96
	herbs	544.98	20.97	-0.79	19.14
Delayed Word Recall *(% accuracy)*	placebo	50.33	3.53	-13.50	3.12
	complete drink	44.50	4.23	0.17	3.43 *
	glucose	51.33	3.69	-15.33	4.45
	caffigur	45.00	4.95	-10.00	5.13
	herbs	48.50	4.52	-9.33	3.07
Word Recognition *(%>chance)*	placebo	73.56	4.28	-7.81	4.14
	complete drink	69.00	3.66	1.66	3.71
	glucose	73.81	4.25	-4.23	3.66
	caffigur	61.33	5.44	12.85	3.95 ***
	herbs	70.33	4.42	-5.67	5.44
Word Recognition Reaction time *(msecs)*	placebo	660.78	23.96	41.76	14.21
	complete drink	714.57	37.55	-25.52	35.31 †
	glucose	682.37	35.84	-5.75	25.29
	caffigur	690.94	39.38	30.98	30.56
	herbs	675.46	33.89	25.36	35.77
Picture Recognition *(%>chance)*	placebo	79.00	3.90	-9.25	4.24
	complete drink	72.00	4.58	-0.75	5.81
	glucose	75.25	3.88	-8.50	4.46
	caffigur	74.75	5.57	-9.25	4.65
	herbs	71.50	4.31	-4.00	4.10
Picture recognition Reaction time *(msecs)*	placebo	744.09	16.32	13.75	15.10
	complete drink	776.72	26.03	-20.08	15.29
	glucose	746.34	34.14	3.31	25.19
	caffigur	753.48	20.62	3.63	15.83
	herbs	768.41	21.94	-0.63	15.48

Fig. 1 Running order of the tasks from the CDR computerised assessment battery, with, to the left, a diagrammatic representation of each task's contribution to the cognitive factors, and to the right, baseline and change from baseline data following each treatment (*t*, $0.05<P<0.1$; $*P<0.05$, $***P<0.005$ compared with corresponding placebo score)

probability, with a randomly varying inter-stimulus interval of between 1 and 3.5 s. Reaction times (ms) and accuracy (%) were recorded.

Spatial working memory A pictorial representation of a house was presented on the screen with four of its nine windows lit. The participant was instructed to memorise the position of the illuminated windows. In 36 subsequent presentations of the house, one of the windows was illuminated and the participant decided whether or not this matched one of the lighted windows in the original presentation. The participant made their response by pressing the "YES" or "NO" response button as quickly as possible. Mean reaction times were measured in milliseconds, and accuracy of responses to both original and novel (distractor) stimuli were recorded as percentages which were used to derive a "% greater than chance performance" score.

Numeric working memory Five digits were presented sequentially for the participant to hold in memory. This was followed by a series of 30 probe digits for each of which the participant decided whether or not it had been in the original series and pressed the "YES" or "NO" response button as appropriate as quickly as possible. This was repeated two further times with different stimuli and probe digits. Mean reaction times were measured in milliseconds, and accuracy of responses to both original and novel (distractor) stimuli were recorded as percentages which were used to derive a "% greater than chance performance" score.

Delayed word recall The participant was again given 60 s to write down as many of the words as possible. The task was scored as number correct, errors and intrusions and the resulting score was converted into a percentage.

Delayed word recognition The original words plus 15 distractor words were presented one at a time in a randomised order. For each word, the participant indicated whether or not he recognised it as being included in the original list of words by pressing the "YES" or "NO" button as appropriate and as quickly as possible. Mean reaction times were measured in millisecond, and accuracy of responses to both original and novel (distractor) stimuli were recorded as percentages which were used to derive a "% greater than chance performance" score.

Delayed picture recognition The original pictures plus 20 distractor pictures were presented one at a time in a randomised order. For each picture, participants indicated whether or not it was recognised as being from the original series by pressing the "YES" or "NO"

button as appropriate and as quickly as possible. Mean reaction times were measured in millisecond, and accuracy of responses to both original and novel (distractor) stimuli were recorded as percentages which were used to derive a "% greater than chance performance" score.

Primary cognitive outcome measures

The above measures were collapsed into the five outcome factors derived from the battery by factor analysis, and the global "Quality of Memory" measure (see Wesnes et al. 2000 for details), as previously utilised by Kennedy et al. (2000, 2001a,b, 2002a,b) and Wesnes et al. (2000). The running order of tasks, the contribution of each individual task outcome to the outcome factors, and baseline and post-drink change from baseline data are represented in Fig. 1.

Memory

"Quality of memory" measure This is derived by combining the "Secondary Memory" and "Working Memory" factor scores (see below).

"Secondary memory" factor This is derived by combining the percentage accuracy scores (adjusted for proportions of novel and original stimuli where appropriate) from all of the secondary memory tests—delayed word recognition, delayed picture recognition, immediate word recall and delayed word recall. One hundred percent accuracy across the four tasks would generate a maximum score of 400 on this index.

"Working memory" factor This is derived by combining the percentage accuracy scores from the two working memory tests—spatial working memory, and numeric working memory. One hundred percent accuracy across the two tasks would generate a maximum score of 200 on this index.

"Speed of memory" factor This is derived by combining the reaction times of the four computerised memory tasks—numeric working memory, spatial memory, delayed word recognition, and delayed picture recognition (units are summed milliseconds for the four tasks).

Attention

"Speed of attention" factor This is derived by combining the reaction times of the three attentional tasks—simple reaction time, choice reaction time and digit vigilance (units are summed milliseconds for the three tasks).

"Accuracy of attention" factor This is derived by calculating the combined percentage accuracy across the choice reaction time and digit vigilance tasks with adjustment for false alarms from the latter test. One hundred percent accuracy across the two tasks would generate a maximum score of 100.

Serial subtraction tasks

A modified computerised version of the Serial Sevens test was utilised. The original verbal Serial Sevens test (Hayman 1942) has appeared in a number of forms, including as part of the Mini-Mental State Examination (Folstein et al. 1975). It has been used to assess cognitive impairment during hypoglycaemia (e.g. Hale et al. 1982; Taylor and Rachman 1987), and has also been used to investigate the relationship between blood glucose levels and cognitive performance (Kennedy and Scholey 2000; Scholey 2001; Scholey et al. 2001) and the acute effects of ginkgo and ginseng (Scholey and Kennedy 2002). In the current study, computerised versions of serial subtractions were implemented (see Scholey et al. 2001 for details), here using tests of 2 min duration. For the Serial Sevens task, a standard instruction screen informed the participant to count backwards in sevens from the given number, as quickly and accurately as possible, using the numeric keypad to enter each response. Participants were also instructed verbally that if they were to make a mistake they should carry on subtracting sevens from the new incorrect number. A random starting number between 800 and 999 was presented on the computer screen, which was cleared by the entry of the first response. Each three-digit response was entered via the numeric keypad with each digit being represented on screen by an asterisk. Pressing the enter key signalled the end of each response and cleared the three asterisks from the screen. The task was scored for total number of subtraction and number of errors. In the case of incorrect responses, subsequent responses were scored as positive if they were correct in relation to the new number.

The Serial Threes task was identical to Serial Sevens, except that it involved serial subtraction of threes.

Treatments

On each study day, participants received one of five 250 ml drinks. The individual drinks comprised: (1) vehicle, containing water as its major constituent, with artificial sweeteners and flavourings to produce a matched placebo, but no active ingredients; (2) vehicle plus 75 mg caffeine (derived from direct addition of caffeine plus guarana extract); (3) vehicle plus 37.5 g glucose; (4) vehicle plus flavouring levels of herbs (12.5 mg ginseng extract and 2.004 mg ginkgo biloba extract); and (5) the complete energy drink containing 75 mg caffeine, 37.5 g glucose and flavouring levels of herbs.

Procedure

Each participant was required to attend a total of 6 study days that were conducted 7 days apart. Testing took place in a suite of laboratories with participants visually isolated from each other. Visits were completed by 12 noon and each participant was tested at the same time on subsequent visits.

During the first session on the first day, participants were allocated to a treatment regime using a Latin square design which counterbalanced the order of treatments across the 5 active days of the study. A person not involved in the trial carried out random allocation to treatment regimens manually using random number tables. The first day was identical to the following 5 days, with the exception that no treatment (active or placebo) was offered. This session allowed familiarisation with the test battery and procedure, and attenuation of any practice effects. Data from the practice day were not included in any analysis.

On arrival at each session, participants completed the first "pre-dose" mood and cognitive performance testing session, which established baseline performance for that day. This was followed by the first heart rate and blood glucose reading, after which participants were allowed up to 5 min to consume the day's treatment (visits 2–6). Heart rate and blood glucose levels were again established 28 min after consumption of the drink. The second testing session began 30 min after consumption of the day's treatment, and was again followed by the final heart rate and glucose level measurement (approximately 60 min post-dose).

Each mood and cognition testing session comprised completion of the Bond–Lader visual analogue scales, and the POMS. This was followed by the DSST, the CDR test battery and finally the Serial Threes and Serial Sevens subtraction tasks.

Statistics

Change from baseline scores from each of the cognitive and mood measures (Bond–Lader, POMS, CDR single tasks and factors, serial subtraction tasks) were initially analysed with a one factor (condition) repeated measures ANOVA. Following the recommendations of Keppel (1991) the omnibus *F*-test was eschewed in favour of planned comparisons, which were made between the placebo condition and each of the four active conditions (complete drink, glucose fraction, herbal fraction, caffeine fraction) utilising *t*-tests incorporating MSError from the ANOVA (analyses of variance were conducted solely to generate appropriate error terms). To ensure the overall protection level all testing was two-tailed, comparisons were strictly planned prior to the study, were restricted to the number of conditions minus one, and only probabilities associated with these pre-planned comparisons were calculated.

Change from baseline heart rate and glucose data were analysed using a two factor (condition×post-dose measurement) repeated measures ANOVA, with planned comparisons being made as above.

Results

Physiological measures

The results of the physiological measures are presented in Fig. 2, which also depicts the timing of the experimental measures.

Heart rate

Following ingestion of the glucose fraction participants heart rates were significantly increased during the final measurement [$t(76)=2.86$, $P=0.005$]. In contrast to this, heart rate was significantly reduced at the same time-point following the caffeine fraction [$t(76)=3.72$, $P=0.0004$], with a trend towards the same effect at 30 min post-dose [$t(76)=1.79$, $P=0.08$] (Fig. 2 a).

Blood glucose levels

Blood glucose levels were significantly raised in comparison with placebo following ingestion of both the complete drink and the glucose fraction at 30 min post-dose ([$t(76)=5.22$, $P<0.0001$] and [$t(76)=7.03$, $P<0.0001$], respectively). In contrast to this the herbal flavouring fraction evinced a reduction in blood glucose levels during the final measurement [$t(76)=2.26$, $P<0.027$] (Fig. 2 b).

Cognitive measures

Digit Symbol Substitution Task

There were no significant differences in performance on this task.

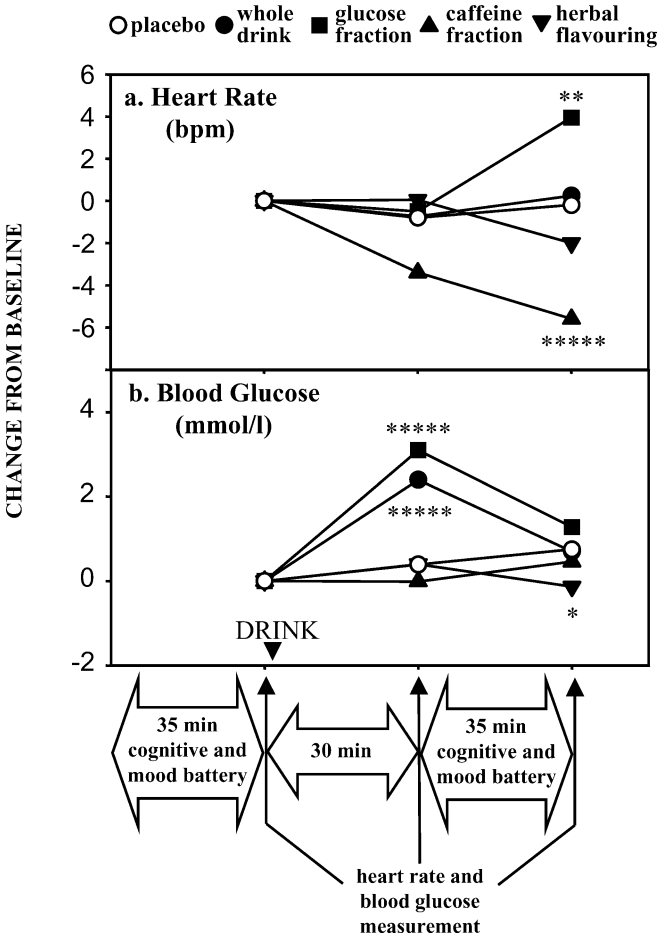


Fig. 2 Effects of treatments on change-from-baseline scores for **a** mean heart rate and **b** mean blood glucose levels. Measures were taken pre-drink (baseline) and before and after the second cognitive assessment. The placebo condition is represented by *empty circles*, the whole drink by *filled circles*, the glucose fraction by *filled squares*, the caffeine fraction by *upward triangles* and the herbal flavouring drink by *downward triangles* (**P*<0.05; ***P*<0.01; ******P*<0.0005 compared to corresponding placebo score). Timings of the experimental phases are also shown

CDR battery

Significant differences on single task outcomes are described below in relation to the primary outcome cognitive factors to which the single task outcome contributes. Pre-drink baseline and change from baseline data are represented in Fig. 3, with graphic representations of change from baseline data for each factor.

Memory

Quality of memory Performance on the global "quality of memory" factor was significantly improved following the complete drink, with the normal decline seen at the second testing session attenuated [$t(76)=2.79$, $P=0.007$]. There was also a trend towards improved performance following the caffeine fraction [$t(76)=1.83$, $P=0.07$].

Task	Condition	Pre-dose score (s.e.)		Change score (s.e.)		
Quality of Memory *(% X 6)*	*placebo*	**446.29**	*12.03*	**-51.24**	*12.21*	
	whole drink	**419.15**	*13.90*	**0.73**	*10.22*	**
	glucose	**440.11**	*12.90*	**-38.88**	*13.94*	
	caff/gur	**414.25**	*17.91*	**-17.08**	*13.86*	t
	herbs	**431.15**	*14.87*	**-35.52**	*13.16*	
Secondary Memory *(% X 4)*	*placebo*	**263.06**	*12.08*	**-41.23**	*10.89*	
	whole drink	**238.00**	*13.82*	**4.58**	*10.29*	**
	glucose	**261.89**	*12.52*	**-34.06**	*11.73*	
	caff/gur	**235.25**	*17.21*	**-13.23**	*11.87*	t
	herbs	**249.50**	*13.83*	**-31.83**	*11.87*	
Working Memory *(% X 2)*	*placebo*	**183.23**	*1.99*	**-10.01**	*5.27*	
	whole drink	**181.15**	*2.92*	**-3.86**	*3.05*	
	glucose	**178.22**	*3.39*	**-4.82**	*4.57*	
	caff/gur	**179.00**	*3.01*	**-3.85**	*5.28*	
	herbs	**181.65**	*2.48*	**-3.69**	*2.58*	
Speed of Memory *(summed msecs)*	*placebo*	**2568.84**	*72.19*	**23.26**	*37.31*	
	whole drink	**2670.23**	*105.66*	**-121.7**	*49.54*	t
	glucose	**2589.17**	*109.45*	**-53.09**	*57.09*	
	caff/gur	**2591.12**	*93.58*	**12.56**	*64.45*	
	herbs	**2548.86**	*77.89*	**26.40**	*80.47*	
Accuracy of Attention (%)	*placebo*	**89.68**	*0.75*	**-1.13**	*0.85*	
	whole drink	**90.20**	*0.63*	**-0.20**	*0.57*	
	glucose	**90.25**	*0.64*	**-2.05**	*0.94*	
	caff/gur	**88.68**	*0.81*	**2.10**	*0.80*	t
	herbs	**89.23**	*1.15*	**-1.90**	*2.23*	
Speed of Attention *(summed msecs)*	*placebo*	**1040.34**	*24.91*	**25.25**	*10.44*	
	whole drink	**1038.48**	*25.69*	**-12.05**	*16.07*	*
	glucose	**1042.71**	*24.21*	**19.64**	*16.65*	
	caff/gur	**1034.52**	*22.45*	**-3.97**	*11.54*	
	herbs	**1036.66**	*25.43*	**24.40**	*12.62*	

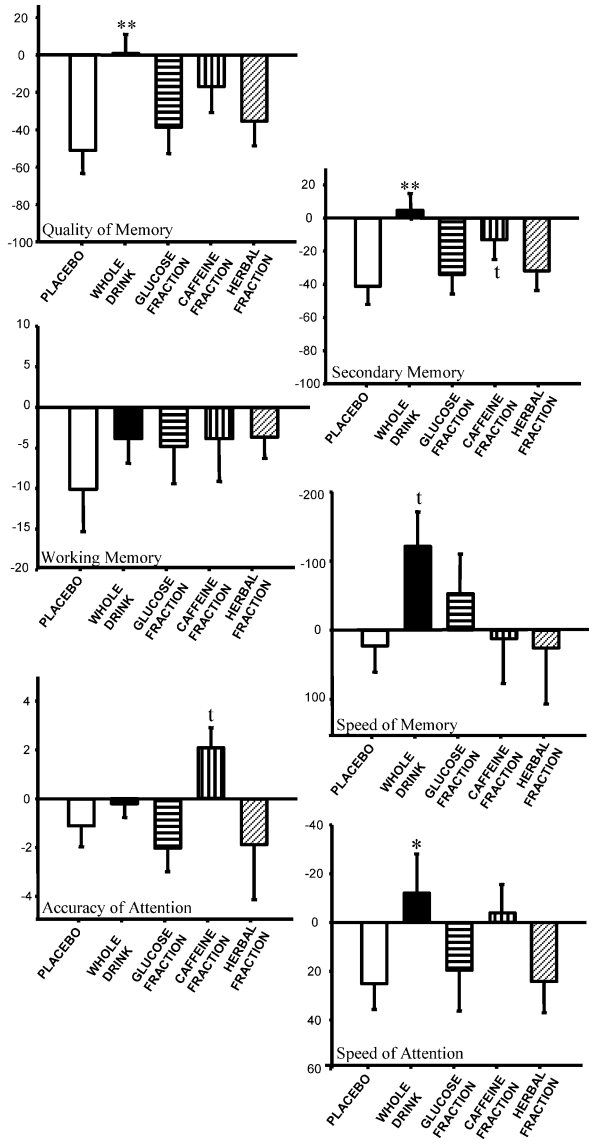


Fig. 3 Baseline and change from baseline data for the primary outcome cognitive factors from the CDR battery, with a graphic representation of the change from baseline data for each factor. The placebo condition is represented by *empty bars*, the whole drink by *filled bars*, the glucose fraction by *horizontally hatched bars*, the caffeine fraction by *vertically hatched bars* and the herbal flavouring drink by *diagonal hatched bars* (t, $0.05<P<0.1$; $*P<0.05$; $**P<0.01$ compared to corresponding placebo score). In every case more positive performance is indicated by an upward change on the y-axis

Secondary memory Performance on the "secondary memory" factor was significantly improved following the complete drink [$t(76)=2.78$, $P=0.007$]. There was also a trend towards improved performance following the caffeine fraction [$t(76)=1.7$, $P=0.09$]. Reference to the single task outcome data showed that following the complete drink participants performed significantly better than following placebo on both the immediate [$t(76)=2.26$, $P=0.027$] and delayed word recall tasks [$t(76)=2.57$, $P=0.012$], whilst the caffeine fraction condition outperformed placebo on the delayed word recognition task [$t(76)=3.37$, $P=0.001$].

Working memory There were no significant differences on the "working memory" factor or the contributing single task outcomes.

Speed of memory Whilst there were no significant differences on this factor, there was a trend towards faster performance for the complete drink condition [$t(76)=1.77$, $P=0.08$]. Examination of the individual outcomes showed that, although only resulting in a trend towards faster performance on one outcome, delayed word recognition [$t(76)=1.72$, $P=0.09$], the complete drink condition outperformed placebo on speed of performing all four contributing tasks.

Attention

Accuracy of attention Whilst there were no significant differences on this factor, there was a trend towards faster performance for the caffeine fraction condition [$t(76)=1.85$, $P=0.07$]. In line with this the same condition evinced a trend towards improved performance on the choice reaction time task [$t(76)=1.81$, $P=0.07$].

Speed of attention Following the complete drink performance was significantly improved on the "speed of attention" factor [$t(76)=2.05$, $P=0.044$]. Although examination of the single outcomes showed that there were no significant differences it is noteworthy that the complete drink tended to improve speed of performance on each of the three contributing tasks.

Serial subtraction tasks

There were no significant differences in performance of the serial subtraction tasks. However, the complete drink condition evinced a trends towards increased number of responses on both the Serial Threes and Serial Sevens tasks [$t(76)=1.73$, $P=0.09$ and $t(76)=1.64$, $P=0.1$, respectively].

Mood measures

There were no significant differences on either the Bond–Lader scales or the POMS. Additionally the 16 scales with make up the Bond–Lader mood scales were analysed separately to allow comparison with Warburton et al.'s (2001) study. Again, no significant treatment effects were revealed.

Discussion

The current study demonstrates that the consumption of a glucose and caffeine containing "energy drink" can improve cognitive performance, in this instance without significant mood changes. In comparison to placebo, significant improvements were seen both on the "secondary memory" factor, and on the "speed of attention" factor derived from the comprehensive selection of tasks from the CDR battery. In both instances, the energy drink led to a net improvement in performance. This general pattern of results supports previous findings of a lack of a direct, selective enhancement of declarative memory tasks by glucose alone (e.g. Azari 1991; Scholey et al. 2001; Ford et al. 2002; Sünram-Lea et al. 2002). However, the addition of a relatively modest amount of caffeine here appears to benefit performance of such tasks.

Neither glucose nor caffeine in isolation resulted in significant improvements of any cognitive or mood measure. The caffeine drink did result in trends towards improved "secondary memory" and "accuracy of attention" performance (as well as similar effects for a number of single tasks). A power analysis was deemed inappropriate for such an exploratory study. However, it is possible that increasing the sample size may have revealed significant effects of caffeine on these measures. Furthermore, in the absence of any direct evidence to the contrary, we cannot preclude the possibility that the small portion of caffeine derived from guarana would have engendered a different profile of effects to those of caffeine from more usual sources.

Interestingly, caffeine alone produced a significant reduction in heart rate at the final reading (and a trend at the 30 min time-point). This is consistent with previous reports of heart rate deceleration associated with consumption of caffeine (Passmore et al. 1987; Pincomb et al. 1991; Quinlan et al. 2000). This effect appears to rely on shifting the equilibrium between two caffeine sensitive systems. The first is adenosine blockade at sympathetic nerve terminals which increases noradrenaline release resulting in heart rate acceleration. The other is the activation of medullary vagal nuclei (directly or via the baroreceptor reflex) which results in heart rate deceleration (Green et al. 1996). It appears that in the present conditions the latter response prevails.

With regard to glucose in isolation, the only significant findings were the anticipated increase in blood glucose levels at the 30 min post-drink time point, and an increase in heart rate at the end of testing. This latter finding is in keeping with previously reported increases in heart rate observed during cognitive processing following a glucose drink (Kennedy and Scholey 2000; Ford et al. 2002). Whilst the general cognitive effects of glucose could be described as being relatively subtle, often being investigated using large sample sizes, one surprise here is a lack of effect on the cognitively demanding Serial Sevens. Performance on this task has been reliably improved by administration of glucose to samples of this size (Kennedy and Scholey 2000; Scholey et al. 2001; Sünram-Lea et al. 2002). However, examination of the blood glucose data suggests that this task, coming as it did at the end of the battery, was performed at a point when blood glucose levels had already fallen towards pre-drink levels. It seems possible that had this task been performed earlier in the battery, it may have benefited from the treatment. Interestingly, the complete drink evinced trends towards increased total responses on both subtraction tasks, and again may reflect the combination effects of caffeine and glucose.

The authors of two previous studies into the cognitive effects of "energy drinks" have acknowledged that other ingredients, including glucose, might have exerted a subtle effect on their results (Alford et al. 2000; Smit and Rogers 2002). However, the findings from such studies are generally ascribed to the caffeine content of the drinks utilised (Alford et al. 2000; Warburton et al. 2001; Reyner and Horne 2002; Smit and Rogers 2002). The results of the present study, designed to disentangle the contribution of the individual drink components to any behavioural effects, suggest that this interpretation may be premature.

Specifically it would appear that the cognition enhancing properties of "energy drinks" should be attributed to the combination of active ingredients rather than solely to caffeine. A related point is that, if caffeine is the major psychoactive agent of the drink, one might expect attentional effects to be more pronounced than those on memory. Here the opposite pattern was found, indeed the effects on attention were marginally significant and it may be that had we used a more conservative comparison this may not have reached statistical significance. However it was felt that such an adjustment was inappropriate in an exploratory study such as this.

Similarly, it seems unlikely that the flavouring levels of herbal extracts utilised here contributed to the overall cognitive effect, given that they were administered at approximately 1–3% of psychoactive doses (see Kennedy et al. 2000, 2002b; Kennedy and Scholey 2003). Indeed in the herbal fraction condition, participants' performance was similar to placebo on all measures apart from blood glucose, where there was a reduction at the final testing point. The relevance of this single finding is difficult to judge, and it remains a possibility that this may reflect a simple type I error. On the other hand it may be a real physiological reaction to the flavour of this drink. For example, it is feasible that the herbal flavourings acted as a (false) signal for a nutritional load, promoting the release of insulin and a consequent uptake of blood glucose. This effect would be masked in the other drink conditions by the higher levels of circulating glucose in both the whole drink and glucose treatments. In the case of the caffeine condition, a history of caffeine ingestion in these regular caffeine drinkers, often in the absence of a nutritional load, would not be expected to elicit such a response. On the other hand, if this was the reason for the drop in blood glucose associated with the herbal fraction, one might expect a similar response to the placebo drink. It is possible that subtle (even sub-threshold) changes in "mouth feel" and taste may account for this disparity.

The present study found no effects of treatment on mood, even when individual items from the Bond–Lader were scrutinised. While this is consistent with the literature on glucose (e.g. Reid and Hammersley 1995), a number of studies have identified modulation of mood by caffeine (e.g. Smith et al. 1994a; Warburton 1995; see Introduction). The reason for this discrepancy is not clear, although it may reflect differences in drink composition or the timing of the mood tests in relation to drink consumption. A further possibility is that the testing situation itself, which included serial blood sampling, may have caused an increase in arousal, since caffeine improvement in alertness is most readily seen in situations of low arousal (see Smith et al. 2003).

Our interpretation of the results as reflecting the effects of the combination of caffeine and glucose does raise the question of potential mechanisms. Both caffeine and glucose may exert their influence, in part, via cholinergic modulation. It has been suggested that caffeine has this effect due to adenosine receptor blockade, resulting (amongst other effects) in an up-regulation of cholinergic activity (Biaggoni et al. 1991; Nehlig et al. 1992), possibly in the ascending cholinergic pathway (Warburton et al. 2001). Additionally, both glucose and caffeine have been shown to reverse scopolamine-associated cognitive deficits (Parsons and Gold 1992; Reidel et al. 1995). In the case of glucose a number of authors have suggested that the memory enhancing effect of glucose may be related to its role as a substrate for the synthesis of acetylcholine (e.g. Wenk 1989; Gold 1995; Sünram-Lea et al. 2002). Previous research indicates that increased cholinergic activity would be expected to produce a pattern of preferential improvements both in the performance of attentional tasks, and in secondary memory tasks (e.g. Rusted 1988; Rusted and Warburton 1988, 1991; Rusted et al. 1991; Blokland 1996). This is consistent with the pattern of enhancement observed here, with significantly improved performance on the "secondary memory" and "speed of attention" factors following the whole drink. This raises the possibility that the combination of glucose and caffeine is increasing cholinergic activity above that seen following either treatment in isolation, with more reliable functional consequences. On the other hand, adenosine blockade affects numerous neurotransmitter systems, and some of caffeine's behavioural effects appear to be modulated by central noradrenergic mechanisms (Smith et al. 2003). Similarly, glucose affects many neurotransmitter and hormonal regulatory systems. The most obvious of these is the promotion of insulin release, an effect which is known to be capable of modulating cognitive function (Park 2001). It therefore seems unlikely that the effects observed here are exclusively underpinned by modulation of cholinergic activity.

A further speculative possibility, given that caffeine has been shown to increase local cerebral glucose consumption at approximately the dose/kg employed here, with activation spreading through the brain with increasing dose (Nehlig and Boyett 2000), is that the simple augmentation of circulating blood borne glucose leads to further increases in cerebral glucose consumption, thus magnifying the localised effects of caffeine. These possible explanations are not mutually exclusive, nor are they meant to be exhaustive. It seems likely that the cognitive effects of nutraceuticals such as the agents assessed here represent a synergistic combination of neurotransmitter, neurohormonal and metabolic effects.

A related point is that, although three of the six cognitive factors were improved by the whole drink, few of the individual contributing tasks were changed significantly. This is in keeping with previous work on nutraceuticals using the CDR battery (Kennedy et al. 2000, 2001a,b, 2002a,b). It may be that this is a feature of the behavioural effects of such agents, that is, they may exert subtle effects on systems underlying single tasks and their benefit may only be seen when such effects are combined. This may have real life implications since day-to-day cognition may involve relatively domain-impure cognitive function. It would therefore be of some interest to assess the effects of these substances on aspects of "everyday" cognition.

Finally it is worth noting that the effects reported here were in individuals who were both caffeine-deprived and who had fasted overnight. Further studies are necessary in order to determine whether the results reflect absolute enhancement or merely a reversal of deprivation states (see Rogers et al. 2003). Nevertheless, if they are the latter, it is obvious that such reversal is differentially affected by caffeine, glucose and their combination. Such effects are clearly worthy of further mechanistic investigation in both deprived and non-deprived individuals. It should also be noted that glucose enhancement of memory (when co-performing a secondary task) is evident when a glucose load is consumed within 2 h of a meal (Sünram-Lea et al. 2001). Additionally we have preliminary data suggesting that caffeine at the dose employed here has similar cognitive effects in caffeine withdrawn and non-withdrawn (habitual non-consumers) individuals (Haskell et al., unpublished data; see also Warburton 1995; Warburton et al. 2001).

In conclusion, the cognitive and mood effects of differing levels of blood glucose, either via direct administration, or by investigations assessing performance under euglycaemic, hyperglycaemic or hypoglycaemic conditions, has attracted a large and expanding body of research. Similarly, the behavioural effects of caffeine are well documented. Nevertheless, the direct comparative or combined effects of the two have not been systematically addressed to date. This is particularly surprising given that glucose and its metabolic products represent the major energy "currency" of all cellular metabolism, whilst caffeine consumption is ubiquitous, with some 86% of the population consuming caffeinated beverages on a regular basis (Hughes and Oliveto 1997). The results of the current study, showing as they do a combined effect for the two agents greater than either of their two parts, suggests that this is an area that would benefit from further research.

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