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ORIGINAL INVESTIGATION

The effect of glucose dose and fasting interval on cognitive function: a double-blind, placebo-controlled, six-way crossover study

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Abstract
Rationale Previous research has identified a number of factors that appear to moderate the behavioural response to glucose administration. These include physiological state, dose, types of cognitive tasks used and level of cognitive demand. Another potential moderating factor is the length of the fasting interval prior to a glucose load.
Objectives Therefore, we aimed to examine the effect of glucose dose and fasting interval on mood and cognitive function.
Methods The current study utilised a double-blind, placebo-controlled, balanced, six period crossover design to examine potential interactions between length of fasting interval (2 versus 12 hours) and optimal dose for cognition enhancement.
Results Results demonstrated that the higher dose (60 g) increased working memory performance following an overnight fast, whereas the lower dose (25 g) enhanced working memory performance following a 2-h fast.
Conclusions The data suggest that optimal glucose dosage may differ under different conditions of depleted blood glucose resources. In addition, glucoregulation was observed to be a moderating factor. However, further research is needed to develop a model of the moderating and mediating factors under which glucose facilitation is best achieved.

Keywords Cognition · Cognitive · Glucose · Metabolism

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Introduction

One under-researched potential modifier of the glucose facilitation effect is the length of fasting interval prior to glucose administration. Studies of glucose and cognition have been conducted using a variety of pre-testing dietary regulations. For example Azari (1991) administered glucose following a standardised breakfast, whereas some researchers have implemented no dietary restrictions at all, e.g., Benton and Owens (1993). However, generally speaking, experimenters have favoured a procedure where participants are tested in the morning after an overnight fast, (e.g., Foster et al. 1998; Hall et al. 1989; Kennedy and Scholey 2000). So far, research assessing the impact of fasting interval on the glucose facilitation effect has yielded disparate results.

A number of studies have shown that missing breakfast negatively impacts on memory performance (Benton and Sargent 1992; Benton and Parker 1998; Geisler and Polich 1992; Smith et al. 1992). Therefore, Martin and Benton (1999) investigated differences in the extent of cognitive facilitation after glucose ingestion in healthy young female participants who had or had not eaten breakfast. The result of the study demonstrated that whilst glucose administra-

tion improved working memory performance after an overnight fast, ingestion of a glucose drink had no effect on performance in participants who had eaten breakfast. Furthermore, ingestion of a glucose-containing drink after an overnight fast resulted in memory performance comparable to those who had consumed breakfast. Martin and Benton concluded that drinking a glucose-containing drink after an overnight fast reverses the negative cognitive consequences of not eating breakfast, but that no further advantages to ingesting an additional glucose drink can be observed if breakfast is eaten. Yet, Sünram-Lea et al. (2001) demonstrated that glucose ingestion improved verbal and spatial long-term memory performance when given either after an overnight fast or after a 2-h fast following breakfast or lunch. These findings suggest that the cognitive facilitation effect of a glucose drink persists under more naturalistic conditions and is not restricted to long fasting durations and morning administration. This indicates that glucose administration is not simply reversing a deficit due to overnight depleted glycogen stores. However, it is important to note that these studies differed not only in the delay between breakfast administration and ingestion of a glucose drink but also in the glucose dosages used. Martin and Benton administered a glucose load of 50 g, whereas Sünram-Lea et al. used a glucose load of 25 g. It is therefore not only necessary to further investigate whether the glucose facilitation effect is simply the result of restoring blood glucose levels after a substantial fast (as suggested by Martin and Benton) or whether increased provisions of glucose in addition to normal food consumption (or after shorter fast duration) produce a similar facilitation of cognition. It also might be the case that different dosages of glucose have their greatest benefit following different fasting intervals.

Consequently, the aim of the current study was to investigate the potential interaction between length of fasting interval (12 versus 2 h) and dose of glucose load (0, 25, 60 g) and to compare the magnitude of the glucose effect on various aspects of cognition. Previously, we have addressed the question of dose dependency of the glucose facilitation effect (Sünram-Lea et al. 2010). Dosages of 0, 15, 25, 50 and 60 g were examined across a number of cognitive tasks. Analysis of the data demonstrated significant glucose facilitation of spatial working memory, immediate and delayed free recall and recognition memory following administration of 25 g of glucose. Discrimination between participants' glucoregulatory status was also investigated, and it was observed that participants with 'good' glycaemic control showed strongest improvements compared with placebo following administration of 60 g of glucose on a serial subtractions task. Overall, the findings demonstrated improved performance following 25 g and reflected the need to continue researching the higher dosage of 60 g. In addition, the current study aimed to investigate the question of domain specificity of cognitive enhancement following glucose administration by assessing various measures of memory, attention and executive function and to examine the potential mediating effects of glucoregulatory response on the glucose facilitation.

Methods

Study population

Thirty healthy young individuals took part in this study. The age range was 18–25 years (mean age 20), and participants had a mean BMI range of 19–24.6 kg/m^2 (22.6 kg/m^2). Participants were recruited via opportunity sampling from the University of Lancaster. Participants were excluded from the study on the basis of several criteria including having diabetes mellitus, phenylketonuria, any food intolerances or allergies, being classed as overweight in accordance with BMI classifications set by the World Health Organisation (e.g., those with a BMI >24.9) or any history of neurological or psychiatric illness or diabetes. Participants received 40 pounds sterling or academic credits for taking part in the experiment. The study was approved by the Lancaster University, Department of Psychology Ethics Committee and conducted in accordance with the Declaration of Helsinki.

Study design and conditions

The study followed a double-blind, placebo-controlled, balanced, six period crossover design. Thirty healthy young adult volunteers were tested under six different experimental conditions the order of which was randomly assigned using a Latin square. The experimental conditions were as follows: (1) 2-h fast and 25 g glucose, (2) 2-h fast and 60 g of glucose, (3) 2-h fast and 0 g glucose, (4) 12-h fast and 25 g glucose, (5) 12-h fast and 60 g glucose and (6) 12-h fast and 0 g glucose.

Treatments

Drinks (which were matched for sweetness) were provided by GSK Nutritionals R&D, Coleford, UK. The drinks contained either 0 g of glucose (placebo drink), 25 g or 60 g of glucose, provided as glucose syrup. All drinks were sweetness matched using artificial sweeteners. Participants in the 2-h fast condition ate a standard breakfast consisting of Kellogg's Rice Krispies® (30 g) with semi-skimmed milk (125 ml) and a 200 ml glass of orange juice. This breakfast provided 51.2 g of carbohydrate (215 kcal) (for further nutritional information, see Table 1).

Table 1 Nutritional information for 30 g serving of Kellogg's Rice Krispies® with 125 ml of semi-skimmed milk

	30 g rice krispies and 120 ml skimmed milk	200 ml orange juice	Total nutrient content of breakfast provided
Energy (kcal)	173	42	215
Protein (g)	6	1	7
Carbohydrate (g)	33	18.2	51.2
Of which sugars (g)	10	18.2	28.2
Starch (g)	23		10
Fat (g)	2.5	0.2	2.7
Of which saturates (g)	1.5	Trace	1.5
Fibre (g)	0.3	0.2	0.5
Sodium (g)	0.25	Trace	0.25
Salt (g)	0.65		0.65

Subjective mood measures

The Bond and Lader visual analogue scales Sixteen visual analogue scales (VAS) (Bond and Lader 1974) were presented on the monitor. Subjective responses were measured via mouse click. Participants were instructed to "use the mouse to position the arrow at the point on the scale that represents how you feel at the present time". The Bond-Lader VAS was administered three times. The first measure was taken before drink administration (baseline). The second measure was taken 20 min following drink consumption to provide a measure of mood prior to cognitive testing after drink administration. The third measure was taken at the end of the testing session 47 min following drink to provide a measure of mood over a longer period of time after cognitive testing.

Cognitive tests

Computerised assessment was used to evaluate cognitive performance. A selection of computer-controlled tasks was administered using Apple Macintosh computer with parallel forms of the tests presented at each test session. For word recall and recognition tasks, the order in which parallel word lists were administered was fully counterbalanced. For other tasks, a random starting number (Serial Subtractions) or random set of stimuli (Corsi blocks, Stroop) were generated at each test. The two reaction time tasks used random inter-stimulus intervals. Task presentation was via VGA colour monitors, and with the exception of written word recall tests, all responses were recorded via key presses. In each session, tests were administered in the following order:

Word Presentation: a list of 20 words matched for frequency, concreteness and imagery was presented on the monitor at the rate of 1 every 2 s for participants to remember. Analogous to previous research (Sünram-Lea et al. 2004, 2010, 2001, 2002a, b), the participants presented with the 20-item word list and were required to perform two types of complex hand motor sequences which were practised with each participant before the first presentation of the word list. Participants were instructed to share their attention equally between the two tasks and were told that they should perform to the best of their ability on each of the two tasks. There were two different motor sequences. Each motor sequence was performed synchronously with both hands. Sequence one comprised 'fist'–'chop'–'slap'. Sequence two consisted of 'back-slap'–'chop'–'fist'. Each participant was instructed to complete one sequence of movements between successive words on the list. Participants were also instructed to change between the two sequences every fifth word; i.e., sequence 1; words 1–5, sequence 2; words 6–10, sequence 1; words 11–15 and sequence 2; words 16–20. Participants were not told the number of words in the list nor when they should change motor sequence. Participants were instructed to remember as many words as they could from the word list whilst carrying out the hand-movement task. The ability of participants to perform the hand-movement task was not formally assessed. The word list was presented twice to participants and immediately recalled after each presentation.

Immediate Word Recall: assessed immediate free recall memory performance of supra-span word list. Participants were given 60 s to write down as many of the words as possible. The task was scored for number correct and number of errors.

Computerized Serial Threes Task: evaluated working-memory performance (Scholey et al. 2001). Participants were required to compute a running subtraction of 3, starting from a randomly generated number. Participants were given 120 s to complete this task.

Computerized Serial Sevens Task: evaluated working-memory performance (Scholey et al. 2001). Participants were required to compute a running subtraction of 7, starting from a randomly generated number. Participants were given 120 s complete this task.

Computerized Corsi Block-Tapping Task: assessed visual memory span (Milner 1971). Illuminated buttons appeared on the screen. Buttons flashed after each other in a tempo of one per second. Participants were then required to point to the buttons in the same order as they appeared on the screen.

Stroop Task: evaluated selective attention and cognitive flexibility (Stroop 1992). Participants were shown 40 colour names (blue, green, red, yellow) printed in coloured ink (blue, green, red, yellow). Participants were instructed to name the colour font in which the colour names are displayed and disregard their verbal content by pressing one of four coloured buttons, with each button representing one of the four colours. For 20 of the stimuli words, the colour of the font was congruent with the semantic meaning of the word. The other 20 words were incongruent. Congruent and incongruent words were presented in random order. Performance was assessed by number of correct responses and reaction time to congruent and incongruent stimuli.

Simple Reaction Time Task: assessed simple reaction time to a visual stimulus (Donders 1868). Participants were presented with the number '1' in the centre of the computer monitor at random time intervals varying from 0.25 ms to1 s. Participants were required to press the number '1' key on the keyboard as fast as they could as soon as the stimulus appeared on the screen. This task took 2 min to complete.

Choice Reaction Time Task: assessed choice reaction time to visual stimuli (Donders 1868). Participants were presented with either the number '1' or the number '2' in the centre of the computer monitor at random time intervals varying from 0.25 ms to 1 s. Participants were required to press either the '1' or '2' key on the keyboard corresponding to the number presented on the screen as fast as they could when the stimuli appear on the screen. This task took 2 min to complete.

Delayed Word Recall: assessed delayed free recall memory performance of supra-span word list. Participants were given 60 s to write down as many of the words as possible. The task was scored as number correct and errors.

Delayed Word Recognition: assessed word recognition. Participant were shown a list of 40 words, 20 of the words were from the previously seen 'word presentation' phase at the beginning of the experiment. The other 20 words were non-target distracter words. Participants were asked to indicate using a 'yes' or 'no' response key press if they had been shown a words previously. The task was scored by number of correct responses and reaction time.

Procedure

Prior to the start of the study, participants were phone screened in order to ensure their suitability for the study; if suitable, treatment order was then randomly allocated with treatments being counterbalanced. Participants were instructed that they should not eat or drink anything (except water) from 12 h prior to testing before attending the laboratory. Each testing session was at the same time of day (beginning either 10 am or 11.00 am). Therefore, those with 10 am timeslots did not eat from 10.00 pm the previous night, and those with 11 am timeslot did not eat from 11 pm the previous night. There was a 1-week washout period between study days. On the first day, participants were provided with a detailed description by the experimenter of what the testing would entail and a study information sheet. They were also shown a list of product ingredients. Participants were then asked to complete a consent form and medical questionnaire and the experimenter measured participants' height and weight. After completion of all necessary paperwork and measurements, depending on the condition to which they were assigned to that week, participants were then given a standard breakfast (2-h fast condition) with glucose administration and cognitive and mood testing carried out 2 h later, or glucose administration and testing commenced immediately (12-h fasting condition). All participants were tested at either 10 am or 11 am (participants always attended the same timeslot for each session); however, on study days when participants were allocated to the 2 h fast condition, they were asked to come into the lab 2 h prior to testing (8 am or 9 am) in order to receive the controlled breakfast meal. During the delay between receiving the meal and testing, participants were instructed to stay in a designated waiting room, where they were allowed to read.

At the start of each test session, participants' baseline glucose levels were measured. They were then asked to rate their current mood state. This was followed by ingestion of the day's treatment following a double-blind procedure. Immediately after drink consumption, the mood scale was administered again. Analogous to the procedure of previous studies (e.g., Foster et al. 1998; Owen et al. 2010; Sünram-Lea et al. 2010, 2002a, b), the first cognitive test was carried out 20 min after drink consumption (in order to ensure successful transfer of glucose to brain). Blood glucose measurements were taken at baseline and approx-

imately 15, 35, and 48 min after drink administration. Each test session comprised completion of the cognitive test battery (cognitive performance) and mood visual analogue scales.

Statistical analyses

Data tables are given as means±standard. Blood glucose values were examined using a three-way repeated measures analysis of variance (ANOVA), the factors being *dose* (0, 25, and 60 g of glucose), *fasting condition* (2-h versus 12-h fast) and *time* (baseline, 15, 35, 48 min). Where interactions were observed, Bonferroni post hoc comparisons were made between glucose and placebo.

All mood and cognitive scores were calculated as change from baseline scores.

Unless otherwise stated, cognitive scores were analysed using two-way repeated measures ANOVA, the factors being *dose* (3 levels; 0, 25, and 60 g of glucose) and *fasting condition* [2 levels; 2-h versus 12-h fast]. Immediate recall and mood scores were analysed by three-way ANOVA: *dose* × *fasting condition* × *trial* (i.e., performance over the course of two trials) for the former and *dose* × *fasting condition* × *time* for the latter. In addition, Dunnett's test for planned (a priori) comparisons between the placebo drink and the two different glucose drinks were conducted.

Results

Glycaemic response

Blood glucose profiles are plotted in Fig. 1. A three-way analysis of variance revealed significant main effects of drink (F (2, 50)=75.30, $p<0.001$) and time (F (3, 75)= 69.82, $p<0.001$). Post hoc comparisons revealed that with the exception of baseline measures at time 0 (baseline), blood glucose values were significantly higher following both the glucose drinks compared to placebo after both a 12-h fast and a 2-h fast (all $p<0.001$). When comparing the glycaemic response between the two glucose drinks, at time 30 (T30) minutes, a glucose load of 60 g led to a significantly higher response than a glucose drink of 25 g following both a 2-h fast ($p=0.009$) and a 12-h fast ($p=$ 0.015). This difference was maintained at time 50 min following a 2-h fast ($p=0.003$). The main effect of fasting interval did not reach significance (F (2, 25)=2.16, $p=0.2$). There was a significant time × drink interaction (F (6, 150)= 33.46, $p<0.0001$) and the time × fast interaction just failed to reach significance (F (3, 75)=2.57, $p=0.06$). No drink × fast interaction was observed (F (2, 50)=0.41, $p=0.67$). However, there was a significant drink × time × fast interaction (F (6, 150)=2.91, $p<0.01$), suggesting that length of fasting interval and glucose dose result in different glycaemic responses. Post hoc comparisons revealed that at T30, blood glucose levels were significantly higher following a 12-h fast compared to a 2 h fast for both 25 g glucose ($p=0.043$) and 60 g glucose ($p=0.018$).

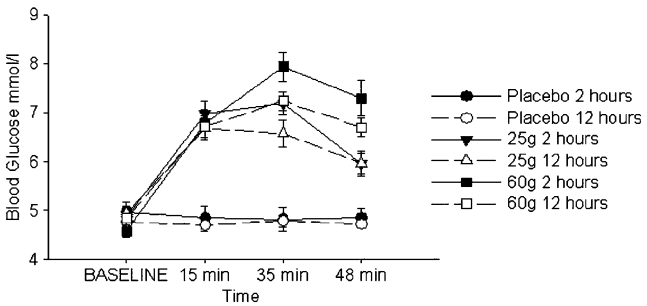

Fig. 1 Glycaemic response as a function of dose and time following a 12-h fast (*broken lines, open symbols*) and 2-h fast (*solid lines, filled symbols*). Compared to placebo, ingestion of glucose led to significant elevation in peripheral blood glucose levels. Circulating glucose levels were higher following 60 g glucose compared with 25 g glucose load and were slightly more elevated following a 12-h fast compared to a 2 h fast (see text)

Subjective mood measures

Alertness: There was a significant main effect of time (F (1, 23)=14.62; $p<0.01$) with participants reporting feeling more alert at time 1 (20 min after drink) compared to time 2 (47 min after drink, the end of the testing session). The main effect of fast (F (1, 23)=4.14; $p=0.05$) revealed that irrespective of drink, participants felt significantly more alert following a 12-h fast compared to a 2-h fast. The drink × fast interaction (F (2, 46)=2.94, $p=0.06$) just failed to reach significance. There was no main effect of drink on alertness (F (2, 46)=0.09, $p=0.92$). Planned t test comparisons with Dunnett correction between glucose and placebo revealed no significant differences between drink and feelings of alertness.

Contentedness: There were no significant main effects of drink and fasting interval and no significant differences between drink and feelings of contentment. There was a significant effect of time on self-rated contentment (F (1, 23)= 10.16, $p<0.01$) with participants feeling significantly more content at time 1 than time 2 irrespective of drink condition.

Calmness: There was a significant interaction between drink × fasting interval (F (2, 46)=4.63, $p<0.02$). Further analysis showed that following overnight fasting, participants reported an overall drop in calmness from baseline scores. Dunnett planned comparisons revealed that this reduction in calmness was significantly greater following placebo than 25 g glucose both at time 1 (t (27)=3.14, $p<0.01$) and time 2

(t (27)=2.83, p<0.05). This effect was also observed after ingestion of 60 g glucose drink compared to placebo at time 1 (t (27)=2.04, p<0.05) and time 2 (t (27)=2.53, p<0.05). No significant main effects of drink, fasting interval or time were observed (Fig. 2; Table 2).

Cognitive performance

See Table 3 for means, SDs and for planned comparisons.

Word Recall: Three-way ANOVA (drink × fast × trial) demonstrated a significant effect of trial of immediate free recall measures (p<.001), with participants' performance significantly improving in the second trial irrespective of drink or fast condition. No other significant main effects or interactions were observed. For delayed free recall performance, no significant main effects or interactions or planned comparisons were observed.

Word Recognition: The drink × fast interaction on word recognition speed for correct responses was marginally significant (F (2, 54)=3.13, p=0.05). Further analysis revealed that after an overnight fast, participants' speed of recognition was significantly faster following administration of 60 g glucose compared to placebo (t (27)=2.52, p< 0.05). There were no significant main effects or interactions on word recognition accuracy.

Serial Threes: There was a significant main effect of drink on the serial three subtractions task (F (2, 54)=4.75, p< 0.02). Further analysis revealed that following an overnight fast, participants performed significantly better in the 60-g glucose condition compared to placebo (t (27)=2.95, p< 0.01) (see Fig. 3).

Serial Sevens: The main effect of drink just failed to reach significance (F (2, 54)=2.87, p=0.07). In addition, there was a trend toward a significant interaction between drink and fasting interval (F (2, 54)=2.93, p=0.06). Dunnett's test for planned (a priori) comparisons revealed that following a 2-h fast, participants performed significantly better in the 25-g glucose condition compared to placebo (t (27)=2.15, p<0.05) (see Fig. 3).

Corsi Block Task: There were no significant main effects of drink on performance nor were there any significant interactions with fast or significant planned comparisons.

Stroop Task: (correct responses and RT) There were no significant main effects of drink on performance nor were there any significant interactions with fast or significant planned comparisons.

Simple Reaction Time Task: There were no significant main effects of drink on performance nor were there any significant interactions with fast or significant planned comparisons.

Choice Reaction Time Task: There was a significant main effect of drink on choice reaction time (F (2, 52)=4.04, p< 0.05) and the drink × fasting interval interaction just failed to reach significance (F (2, 52)=2.25, p=0.08). However, further analysis revealed that following an overnight fast choice reaction time for correct responses was significantly faster in the placebo condition compared to 25 g of glucose (t (27)=2.45, p<0.05). No main effects or interactions were observed on number of correct responses.

Post hoc division of sample based on glucose regulatory indices

Area Under the Curve: The moderating effects of glucose regulation were assessed by calculation of area under the curve (AUC) of evoked glucose levels. Glucose regulation has been routinely indexed using AUC (Moore et al. 2000; Kaplan et al. 2000; Potteiger et al. 2002; Convit et al. 2003). However, differences in the calculations have been noted. We therefore elected to examine two formulae for computation of the area under the curve: (1) AUC with respect to increase (AUC_I) and (2) AUC with respect to ground (AUC_G) (Pruessner et al. 2003). It has been suggested that both formulae reveal different information with AUC_G being related to total output (i.e., taking into account basal glucose levels), and AUC_I being related to sensitivity of the system (i.e., glycaemic reaction to glucose load). Utilising these two measures, we have previously observed differences in their degree of moderation of performance and mood measures (Sünram-Lea et al. 2010).

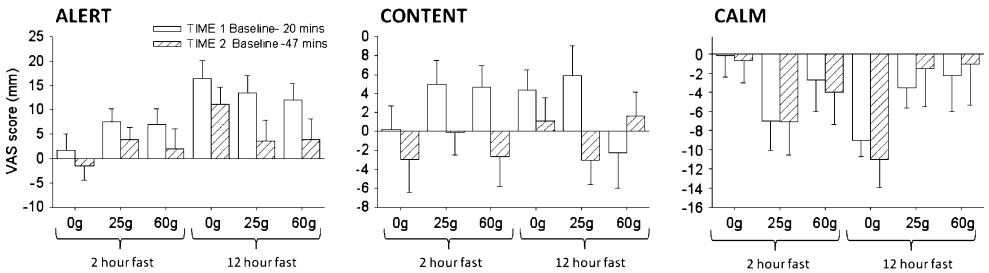

Fig. 2 Subjective alertness, contentment and calmness as a function of dose and time following a 2-h fast and a 12-h fast

Table 2 Drink and fast duration effects on subjective mood measures (means±SD) and *p* values from paired contrasts with between treatment and placebo conditions

	Drink	Baseline	Time 1 Change from baseline	*p* value	Time 2 Change from baseline	*p* value
Alertness						
2-h fast	Placebo	56.94±15.54	1.69±16.54		−1.47±14.57	
	25 g	51.38±14.18	7.55±13.06		3.81±12.17	<0.05
	60 g	55.13±19.03	6.96±15.66		1.94±20.37	
12-h fast	Placebo	41.49±19.05	16.42±18.92		11.04±17.72	
	25 g	47.87±20.04	13.50±17.50		3.54±20.73	
	60 g	48.09±22.10	11.95±16.87		3.89±20.99	
Contentedness						
2-h fast	Placebo	64.30±14.57	0.19±12.29		−2.92±17.28	
	25 g	59.94±13.52	4.96±12.42		−.109±11.56	
	60 g	65.72±16.92	4.67±11.1		−2.64±15.6	
12-h fast	Placebo	60.07±13.38	4.40±10.15		1.12±11.80	
	25 g	61.68±18.56	5.92±15.09		−3.00±12.75	
	60 g	61.28±16.41	−2.22±18.47		1.66±12.30	
Calmness						
2-h fast	Placebo	60.93±11.86	−0.14±11.04		−0.70±11.25	
	25 g	63.41±15.43	−7.00±7.00		−7.10±16.75	
	60 g	60.70±16.16	−2.71±16.23		−3.95±16.68	
12-h fast	Placebo	71.70±12.99	−9.00±8.33		−11.00±14.30	
	25 g	64.94±17.95	−3.54±10.31	<0.005	−1.47±19.79	<0.01
	60 g	64.02±14.43	−2.71±18.47	<0.05	−1.04±20.94	<0.05

Data from the higher glucose load (60 g) following a 12-h fast was used to calculate AUC_G and AUC_I, since this condition most closely resembled the protocol of oral glucose tolerance test (i.e., overnight fast followed by administration of 75 g of glucose).

This was followed by post hoc division of all participants into three equal groups depending on glucoregulation (n=10 per cell). The three divisions of AUC_G were as follows; low (≤62.00), middle (62.01 to 98.00), high (>98.01). The three divisions of AUC_I were as follows; low (≤−0.63), middle (−0.62 to 0.36), high (>0.37). A low AUC score signified good glucoregulation, a middle score signified average glucoregulation, while a high score could be indicative of poor glucoregulation.

For mood measures, four-way ANOVAs were conducted, where *dose* (0, 25, or 60 g) and *fast* (2 or 12 h) and *time* (time 1 and 2) were within-participants factors, and *glucoregulation* (good, average or poor) was a between-participants factor. For cognition, three-way ANOVAs were conducted, with *dose* and *fast* as within-participants factors, and *glucoregulation* as the between-participants factor. Where sphericity could not be assumed, the Greenhouse–Gessier correction was applied and in order to examine main effects and interactions, the Bonferroni corrections post hoc test was used. For analyses of post hoc division of sample, only significant effects and interactions of AUC or those nearing significance level are reported.

Glucoregulatory Indices and Mood: Glycaemic control based on AUC_G and AUC_I had no significant effect on alertness or contentedness, but a significant main effect of AUC_G on feelings of calmness (F (2, 21)=4.183, p=.030) was observed. Post hoc comparison revealed that those in the high AUC group reported a significant decrease in calmness compared to those in low AUC band (p=0.033).

Glucoregulatory control and cognition

Word Recall and Recognition: A significant fast × AUC_I interaction was observed for immediate free recall trial 2 (F (2, 25)=3.469, p=0.047). Post hoc comparison revealed that following an overnight fast, those in the low AUC_I group (good glucoregulation) performed significantly better than those in the high AUC_I group (poor glucoregulation) irrespective of drink (mean performance level 7.267 (SE= 0.393) and 5.886 (SE=0.414), respectively; p=0.03). In addition, there was a significant fast × AUC_I interaction for

Table 3 Drink and fast effects on cognitive performance (means±SD)

Drink	2-h fast (means±SD)	*p* value	12-h fast (means±SD)	*p* value
Word Recall				
Immediate 1				
0 g	4.40±1.70		4.40±2.14	
25 g	4.48±1.74		4.03±1.87	
60 g	4.46±1.62		4.46±1.75	
Immediate 2				
0 g	6.30±2.52		6.77±2.75	
25 g	6.48±2.40		6.06±1.94	
60 g	5.90±1.92		6.57±1.87	
Delayed				
0 g	5.10±1.83		4.57±2.75	
25 g	4.75±1.84		4.40±2.46	
60 g	4.15±1.89		4.62±1.96	
Word Recognition				
Accuracy				
0 g	30.18±4.14		29.51±4.18	
25 g	28.93±4.27		28.92±3.87	
60 g	29.07±4.88		29.68±3.09	
Speed (ms)				
0 g	0.923±0.190		0.938±0.193	
25 g	1.040±0.602		0.970±0.287	
60 g	0.953±0.953		0.851±0.174	<0.05
Serial Sevens				
0 g	18.02±11.47		17.91±10.88	
25 g	24.51±17.69	<0.05	18.46±11.78	
60 g	18.57±11.74		19.71±12.56	
Serial Threes				
0 g	30.42±16.82		30.56±18.41	
25 g	36.10±18.68		33.35±19.94	
60 g	33.60±15.49		37.92±15.46	<0.01
Corsi Block				
0 g	5.49±.96		5.48±1.42	
25 g	5.81±.66		5.70±.75	
60 g	5.62±.62		5.64±.82	
Simple Reaction Time				
0 g	0.365±0.05		0.400±0.134	
25 g	0.356±0.04		0.391±0.107	
60 g	0.403±0.18		0.398±0.154	
Choice Reaction Time				
Accuracy				
0 g	71.10±3.83		71.67±4.03	
25 g	70.32±4.34		70.59±3.78	
60 g	70.74±3.92		71.01±3.77	
Speed				
0 g	0.453±0.063		0.452±0.070	
25 g	0.457±0.063		0.478±0.096	<0.05
60 g	0.463±0.081		0.456±0.076	
Stroop Congruent				
Accuracy				
0 g	148.83±26.39		152.74±24.34	
25 g	153.60±27.45		153.00±31.74	
60 g	150.55±29.08		158.01±33.75	
Speed (ms)				
0 g	0.803±0.161		0.780±0.161	
25 g	0.773±0.174		0.789±0.224	
60 g	0.813±0.301		0.780±0.323	
Stroop Incongruent				
Accuracy				
0 g	140.68±28.38		144.52±23.12	
25 g	142.64±20.93		145.00±26.20	
60 g	143.62±21.81		147.39±24.91	
Speed				
0 g	0.869±0.261		0.762±0.238	
25 g	0.810±0.138		0.199±0.162	
60 g	0.814±0.140		0.801±0.179	

delayed word recall (F (2, 25)=3.578, p=0.043). Again, the observed significant interaction was due to those in the low AUC_I group performing better than those in the high AUC_I group after an overnight fast (mean performance levels 5.373 and 3.493, respectively; p=0.004). Moreover, there was a significant fast × AUC_G interaction on speed of recognition (F (2, 24)=3.809, p=0.039). This did not withstand post hoc testing, but examination of the means showed that those with a low AUC_G had faster reaction times after an overnight fast compared to those with a high AUC_G (mean performance levels 0.837 (SE=0.058) and 0.915 (SE=0.058), respectively), and they also performed better following an overnight fast compared to 2-h fast (1.014 (SE=0.067)).

Working Memory: There was a significant fast × AUC_G interaction on spatial working memory (F (2, 25)=3.571, p=0.042). The observed significant interaction did not withstand post hoc analysis; however, inspection of the means showed that whereas participants with a medium AUC did not differ in performance after 2 h fast compared to 12 h fast (5.774 (SE=0.184) and 5.807 (SE=0.242), respectively), those in the high AUC group showed performance decrements after 12 h fast compared to 2 h fast (5.388 (SE=0.242) and 5.785 (SE=0.184), respectively).

Attention: A significant fast × drink × AUC_G interaction was observed for accuracy on the choice reaction time task (F (4, 48)=2.819, p=0.035). Post hoc comparisons showed that following a 2-h fast, those with a medium AUC_G performed better than those with a low AUC_G following administration of 25 g of glucose (72.375 (SE=1.457) and 68.160 (SE=1.303), respectively; p=0.026). No other meaningful significant differences emerged.

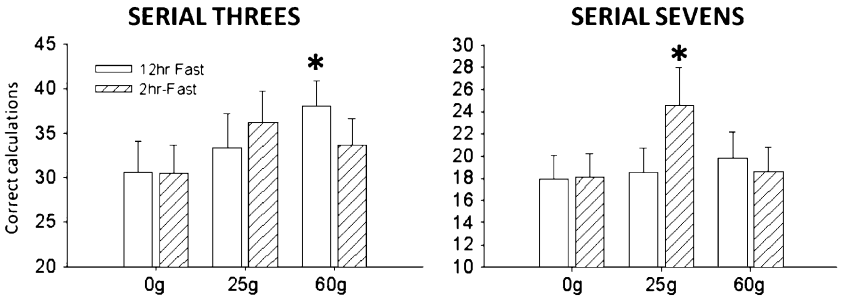

Fig. 3 Performance of serial subtractions as a function of dose and fasting interval following 60 g glucose participants performance was significantly improved compared to placebo following a 12-h fast (*left*). Following 25 g glucose, participants' performance was significantly improved compared to placebo following a 2-h fast (*right*)

Discussion

The primary aims of the present study were to investigate the potential interaction between length of fasting interval (12 versus 2 h) and dose of glucose load (0, 25, 60 g) and to compare the magnitude of the glucose effect on various aspects of cognition. In addition, we aimed to investigate the question of domain specificity of cognitive enhancement following glucose administration by assessing various measures of memory, attention and executive function and to assess the potential mediating effects of physiological response on the glucose facilitation of cognition effect by looking at individual glucose tolerance.

In regard to the glycaemic response, as expected, ingestion of both glucose drinks resulted in a significant rise in blood glucose levels. By contrast, there was no significant rise in blood glucose levels after the ingestion of a placebo drink. Fasting interval did not alter baseline blood glucose levels, demonstrating that blood glucose levels had returned to baseline levels 2 h after ingestion of the breakfast meal. However, breakfast administration did alter the glycaemic response profile as following both glucose drinks blood glucose levels were significantly higher after a 12-h fast compared to a 2-h fast 30 min after drink consumption.

Turning to mood measures, participants rated themselves as more alert following consumption of all drinks, independent of glucose content. Participants felt more content after any of the drinks (regardless of glucose dose) 20 min post ingestion compared to time 47 min. At time, 20 feelings of contentment were overall higher than baseline, whereas at time, 47 feelings of contentment were lower than baseline, suggesting that potential effects on contentment were short lived. Participants also felt less calm following all drinks. However, following a 12-h fast, the reduction in calmness was significantly attenuated after both glucose drinks compared to placebo. These effects were present both 20 and 47 min after ingestion. Reduced calmness coupled with increased alertness may reflect some negative response to aspects of the testing session such as finger-prick blood sampling or cognitive testing. Alternatively, these effects may be due to participants' hydration or food deprivation status. Previously, water ingestion has been found to improve subjective alertness in healthy young who were either relatively thirsty (Rogers et al. 2001) or overnight dehydrated (Neave et al. 2001). Here, effects on mood may have been influenced by the level of food deprivation in as much as participants reported greater increase in alertness following drink consumption (regardless of glucose content) after a 12-h fast compared to a 2-h fast; in both cases, they were allowed to consume water ad libitum. In the current study, thirst and appetite ratings were not taken, in future studies the use of such scales may help to delineate some of the interactions between fast duration and mood responses to drinks.

Overall, it appears that shortly after administration of any of the drinks, participants felt more alert and content. This effect was not maintained at the later time point (the end of the testing session), which suggests that regardless of nutritional content, the effects on alertness and contentment are short lived. Furthermore, feelings of calmness dropped throughout testing; however, this drop was significantly lessened by both glucose drinks, suggesting that glucose curtailed the negative feelings associated with the testing session.

In terms of cognitive performance, following a 2-h fast, the 25-g drink resulted in enhanced performance on the demanding working memory task (serial sevens task) compared to placebo. When participants had fasted overnight, their performance on the less demanding working memory task (serial threes) and speed of recognition was improved following administration of the 60-g glucose drink compared to placebo.

A number or studies have demonstrated glucose enhancement of numeric working memory in the form of serial subtractions. Several studies have demonstrated that following a 12-h fast, administration of 25-g glucose is able to significantly enhance performance of the more demanding serial sevens subtractions task (Kennedy and Scholey 2000; Scholey et al. 2001), while failing to enhance the less

demanding serial threes subtractions task (Kennedy and Scholey 2000; Scholey and Kennedy 2004) (with glucose loads of 25 and 37.5 g, respectively). Kennedy and Scholey argued that the level of cognitive demand is an important moderating factor in the glucose paradigm. In the present study, an effect of serial threes was observed following an overnight fast after consumption of the higher glucose load (60 g) compared to placebo. It may be the case that in order to observe glucose enhancement of less demanding tasks, fasting must be prolonged and a higher dosage may be necessary. A study by Reay et al. (2006) demonstrated that following 25 g of glucose, significantly more serial three subtractions were made in the third, fourth and sixth cycles of a cognitive demand battery consisting of Serial Threes, Serial Sevens and Rapid Visual Information Processing. Reay et al. (2006) argue that the beneficial effect of glucose only becomes apparent as fatigue increases during repeated completions of the task. That is to say, the glucose facilitation effect becomes more apparent as the margins for improvement become greater through fatigue and/or metabolic depletion in the absence of glucose loading. It may be the case that lower level of cognitive demand within a task requires either a higher initial dosage of glucose or that the effects can become apparent only when level of fatigue creates sufficient decrements in energy resources to observe the benefits of glucose supplementation.

Sünram-Lea et al. (2004) and Sünram-Lea et al. (2002a) demonstrated significant improvement of Serial Sevens following 25 g glucose compared to placebo. In these two studies, participants' fasting duration was limited to 2 h, and they displayed blood glucose trajectories typical of a 2-h fast indicating compliance. The findings of the present study, that Serial Sevens task performance is augmented following 25 g glucose after a 2-h fast, are in line with the findings of Sünram-Lea et al., though, failure to observe facilitation of serial sevens following an overnight fast is unexpected since robust effects have been observed on this task following a 12-h fast. Nevertheless facilitation of numeric working memory was observed in this study. It seems strange that the glucose facilitation effect is often observed for the serial subtractions task whereas there seems to be little effect of glucose on other numeric short-term and working memory tasks. Foster et al. (1998)) and Sünram-Lea et al. (2001)) failed to observe significant differences in performance on the digit span task (forwards and backwards) following a 25-g glucose load compared with placebo. Scholey and Kennedy (2004) also observed no performance difference on a number identification task (involving the identification of target digits among probe digits) between a 37.5-g glucose load and placebo. Sünram-Lea et al. (2002b) suggested that the observation of a significant glucose effect on serial subtractions might be related to long-term memory processes, as arithmetical fluency could be related to retrieval from long-term memory. Sünram-Lea et al. (2002b) cited a theory by (Allen et al. 1996) that retrieval may be the common denominator of the glucose facilitation effect. Sünram-Lea et al. (2002b) suggest that aspects of cognition demonstrating a glucose-related facilitation are similar in that they place high demands on retrieval of previously learned information. Therefore, the action of glucose on serial sevens and threes may possibly provide further evidence in favour of the fractionation of the glucose memory enhancement effect, with aspects of memory relating to hippocampal mediation being involved in the glucose effect. However, in the present study, we failed to observe glucose facilitation for any of the verbal memory tasks. This is unexpected since previous research has observed robust effects of glucose on verbal memory (Foster et al. 1998; Sünram-Lea et al. 2001, 2002b, 2010). An effect of word recognition speed was observed in which 60 g glucose resulted in faster reaction times compared to placebo following an overnight fast suggesting that for recognition speed, under conditions of greater depletion of glucose resources participants might benefit from a higher glucose load. While effects of glucose on word recall are generally regarded as ‘robust’, a number of studies have failed to observe effects of glucose (25–50 g) on immediate word recall (Craft et al. 1994; Ford et al. 2002; Foster et al. 1998; Green et al. 2007; Scholey et al. 2001; Scholey and Kennedy 2004; Winder and Borrill 1998) and delayed word recall (Craft et al. 1994; Messier et al. 1999; Scholey and Kennedy 2004; Winder and Borrill 1998; Scholey et al. 2009a).

Messier et al. (1999) reported that the effects of 50 g glucose on free word recall was dependent on glucoregulatory processes, where glucose ingestion reversed the performance decrement associated with poor glucoregulation but did not impact on participants with better glucoregulation. Failure to observe effects of glucose on some of the cognitive measures more robustly associated with enhancement by glucose suggest that moderating factors may be exerting some influence. Messier et al. pointed out that falling or rising blood glucose levels subsequent to the administration of a glucose drink can only be used to categorise participants relative to one another. This recovery index is not an absolute measure of glucose regulation or insulin sensitivity and should not be used as an indicator of how much glucose is successfully transferred to and used in the brain. Therefore, to repeat this caveat, the glucoregulatory measurements used in the present study are not direct measures and only provide a proxy for glucose response and insulin sensitivity. Furthermore, circulating peripheral blood glucose values are not a direct measure of transport and conveyance from blood to brain.

The two indices used in the current study to assess glucoregulatory status index revealed different information from the blood glucose levels. Where AUC_G relates to overall peripheral glucose levels, AUC_I relates solely to response output, as this calculation of area under the curve removes baseline measures from the calculation. It may be the case that in this context, AUC_I is a crude index for the competence of the individual's insulin response to the acute administration of glucose. The calculation for AUC_G measures the area under the curve from ground (zero) including the area up to baseline. An individual's baseline glucose level is likely to reflect the individuals more long-term insulin resistance. Therefore, AUC_G in this context could be taken to provide a combined measure of short-term acute insulin response and more long-term insulin resistance. Predictably, the data demonstrated some disassociation between the effects observed from the different calculations of glucoregulatory indices (AUC_G and AUC_I). It should be noted that glucoregulatory status can also be indexed using a number of other indexes such as HOMA, QUICKI and ISIcomp (see, e.g., Pacini and Mari 2003). These index measures require the knowledge of concurrent insulin levels (from venous blood) which were not collected in the current study. It may be useful to compute and compare indices which include insulin levels in future studies.

In terms of mood measures, glycaemic control based on AUC_G and AUC_I had no significant effect on alertness or contentedness. However, participants with a low AUC_G (good glucose regulation) reported feeling significantly more calm than those with a high AUC_G (poor glucoregulation). Consequently, glucoregulatory status appeared to exert a direct effect on how calm people felt, the mechanism underlying these effects are unknown; however, it is worth noting that hyperglycaemia in type 2 diabetes is characterised by increased 'tense arousal'—i.e., feeling anxious/nervous versus relaxed/calm (Sommerfield et al. 2004).

In terms of memory, for immediate and delayed free recall following an overnight fast, those with better glucose regulation (low AUC_I group) performed significantly better compared to those with poorer regulation (the high AUC_I group) irrespective of drink. Similarly, those with better glucose regulation (low AUC_G) had faster reaction times after an overnight fast compared to those with poorer regulation (high AUC_G), and they also performed better following an overnight fast compared to 2-h fast. For spatial working memory, participants with average glucoregulatory control (medium AUC_G band) did not differ in performance after 2 h fast compared to 12 h fast, whereas those in the high AUC_G group showed performance decrements after 12 h fast compared to 2 h fast. In the choice reaction time task following a 2-h fast, those with average glucose control (medium AUC_G) performed better than those with better glucose regulation (low AUC_G) following administration of 25 g of glucose.

Taken together, the moderating effects of both indices build a picture of how glucoregulation affects mood and cognition. Those with good glucoregulation appear to feel calmer, perform better and faster than to those with poor glucoregulation regardless of drink. In the case of spatial memory, those with poor glucoregulation even appear to show performance decrements compared to those with better glucoregulation.

This is in line with previous findings demonstrating that poorer glucose tolerance in middle aged and elderly participants is associated with reductions in memory performance of immediate and delayed memory performance on the Wechsler Paragraph Recall Test (Convit et al. 2003). Furthermore, in this study, they observed that those with poorer glucose tolerance had smaller hippocampal volumes suggesting atrophy of the hippocampus, an area which is key in recent memory formation (Eichenbaum et al. 1994; Squire and Zola-Morgan 1991; Squire 1992). In the present study, it is noteworthy that the superior performance of those with good glucoregulation compared to poor glucoregulation was observed largely on tasks of verbal declarative memory, which is heavily reliant on the hippocampal formation. The study by Convit et al. (2003) looked at glucoregulation and cognition in healthy elderly participants, and it is interesting that in the present study, young adults with poor glucoregulation also display poorer memory performance.

The only effect drink had on cognition across the different glucoregulation bands was in the choice reaction time task in which those with average glucoregulation performed better than those with a good glucoregulation following administration of 25 g of glucose. Previous research has failed to observe effects of glucose on reaction times. For example, any effect of 37.5 g of glucose supplementation on serial reaction time tasks or choice reaction time tasks compared to the placebo. In one study, a pure carbohydrate solution at breakfast actually impaired serial reaction times (Cunliffe et al. 1997). The results here suggest that glucoregulation may be an important modifier of the effect of glucose on reaction time.

Overall, when comparing the two indices, AUC_I was more predictive of declarative memory whereas AUC_G predicted performance of working memory and reaction times. Several glucoregulatory indices have been previously evaluated for their relationship with cognitive performance in younger and older participants. These include various estimates of glucoregulation such as: fasting levels, peak glucose levels, recovery and evoked glucose to baseline levels and AUC (Craft et al. 1994; Craft et al. 2000; Donohoe and Benton 1999; Kaplan et al. 2000; Manning et

al. 1990; Messier et al. 1997; Parsons and Gold 1992; Vanhanen and Soininen 1998). Generally, area under the curve (AUC) has been assessed as incremental AUC (for example, (Awad et al. 2002). This calculation corresponds to what is termed AUC *increase* by Pruessner et al. (2003). In the present study, we also evaluated AUC *ground* and found disassociations between the two indices. The data from this study tentatively suggest that the two measures may predict performance on different memory domains; however, further study should be made to assess the usefulness of these two indices of glucoregulation in order to ascertain an appropriate proxy of an individual's glucoregulatory status which may then be used more routinely as standard throughout research in this field. It may also be worth noting that the present study utilised a sample of 30 participants which were split into tertiles for analysis of glucoregulatory status. Future research may reveal greater moderating effects if, in a larger sample, the extreme quartiles of glucoregulatory status were examined.

Overall, regardless of nutritional content, all drinks appeared to have short-term beneficial effects on mood. Therefore, it seems likely that palatability or thirst affects mood measures following a drink administration (Scholey et al. 2009b).

In terms of the benefits of a glucose drink on cognitive performance, drink effects for the 60-g dose were strongest after an overnight fast, whereas the lower dose improved performance following a 2-h fast. Therefore, the present findings suggest that under conditions of greater depletion of glucose resources, participants might benefit from a higher glucose load.

Glucoregulation affected mood and cognition in that those with good glucoregulation appear to feel calmer, perform better and faster than to those with poor glucoregulation regardless of drink. Glucoregulatory status affected response to glucose load suggesting that glucoregulation may be an important modifier of the effect of glucose on reaction time.

References

Allen JB, Gross AM, Aloia MS, Billingsley C (1996) The effects of glucose on nonmemory cognitive functioning in the elderly. Neuropsychologia 34:459–465

Awad N, Gagnon M, Desrochers A, Tsiakas M, Messier C (2002) Impact of peripheral glucoregulation on memory. Behav Neurosci 116:691–702

Azari N (1991) Effects of glucose on memory processes in young adults. Psychopharmacology 105:521–524

Benton D, Owens DS (1993) Blood glucose and human memory. Psychopharmacology 113:83–88

Benton D, Parker PY (1998) Breakfast, blood glucose, and cognition. Am J Clin Nutr 67:772S–778S

Benton D, Sargent J (1992) Breakfast, blood glucose and memory. Biol Psychol 33:207–210

Bond A, Lader M (1974) The use of analogue scales in rating subjective feelings. Br J Med Psychol 47:211–218

Convit A, Wolf OT, Tarshish C, De Leon MJ (2003) Reduced glucose tolerance is associated with poor memory performance and hippocampal atrophy among normal elderly. Proc Natl Acad Sci USA 100:2019–2022

Craft S, Murphy C, Wernstrom J (1994) Glucose effects on complex memory and non-memory tasks: the influence of age, sex and glucoregulatory response. Psychobiology 22:95–105

Craft S, Asthana S, Schellenberg G, Baker L, Cherrier M, Boyt AA, Martins RN, Raskind M, Peskind E, Plymate S (2000) Insulin effects on glucose metabolism, memory, and plasma amyloid precursor protein in Alzheimer's disease differ according to apolipoprotein E genotype. Ann N Y Acad Sci 903:222–228

Cunliffe A, Obeid O, Powell-Tuck J (1997) Post-prandial changes in measures of fatigue: effect of a mixed or a pure carbohydrate or pure fat meal. Eur J Clin Nutr 51:831–838

Donders F (1868) On the speed of mental processes. Translated by WG Koster, 1969. Acta Psychol 30:412–431

Donohoe RT, Benton D (1999) Declining blood glucose lelvels after a cognitively demanding task predict subsequent memory. Nutr Neurosci 2:413–424

Eichenbaum H, Otto T, Cohen N (1994) Two functional components of the hippocampal memory system. Behav Brain Sci 17:449–517

Ford C, Scholey A, Ayre G, Wesnes KA (2002) The effect of glucose administration and the emotional content of words on heart rate and memory. J Psychopharmacol 16:241–244

Foster JK, Lidder PG, Sünram SI (1998) Glucose facilitation of memory performance in normal young participants: fractionation of enhancement effects? Psychopharmacology 137:259–270

Geisler MW, Polich J (1992) P300, food consumption, and memory performance. Psychophysiology 29:76–85

Green M, Taylor M, Elliman N, Rhodes O (2007) Placebo expectancy effects in the relationship between glucose and cognition. Br J Nutr 86:173–179

Hall JL, Gonder-Frederick LA, Chewning WW, Silveira J, Gold PE (1989) Glucose enhancement of performance on memory tests in young and aged humans. Neuropsychologia 21:1129–1138

Kaplan RJ, Greenwood CE, Winocur G, Wolever T (2000) Cognitive performance is associated with glucose regulation in healthy elderly persons and can be enhanced with glucose and dietary carbohydrates. Am J Clin Nutr 72:825–836

Kennedy DO, Scholey AB (2000) Glucose administration, heart rate and cognitive performance: effects of increasing mental effort. Psychopharmacology 149:63–71

Manning CA, Hall JL, Gold PE (1990) Glucose effects on memory and other neuropsychological tests in elderly humans. Psychol Sci 1:307–311

Martin PY, Benton D (1999) The influence of a glucose drink on a demanding working memory task. Physiol Behav 67:69–74

Messier C, Gagnon M, Knott V (1997) Effect of glucose and peripheral glucose regulation on memory in the elderly. Neurobiol Aging 18:297–304

Messier C, Desrochers A, Gagnon M (1999) Effect of glucose, glucose regulation, and word imagery value on human memory. Behav Neurosci 113:431–438

Milner B (1971) Interhemispheric differences in the localization of psychological processes in man. Br Med Bull 27:272–277

Moore MC, Cherrington AD, Mann SL, Davis SN (2000) Acute fructose administration decreases the glycemic response to an oral glucose tolerance test in normal adults. J Clin Endocrinol Metab 85:4515–4519

Neave N, Scholey A, Emmett J, Moss M, Kennedy DO, Wesnes KA (2001) Water ingestion improves subjective alertness, but has no effect on cognitive performance in dehydrated healthy young volunteers. Appetite 37:255–256

Owen L, Finnegan Y, Hu H, Scholey AB, Sünram-Lea SI (2010) Glucose effects on long-term memory performance: duration and domain specificity. Psychopharmacology 211:131–140

Pacini G, Mari A (2003) Methods for clinical assessment of insulin sensitivity and [beta]-cell function. Best Pract Res Clin Endocrinol Metab 17:305–322

Parsons MW, Gold PE (1992) Glucose enhancement of memory in elderly humans: an inverted-U dose–response curve. Neurobiol Aging 13:401–404

Potteiger J, Jacobsen D, Donnelly J (2002) A comparison of methods for analyzing glucose and insulin areas under the curve following nine months of exercise in overweight adults. Int J Obes 26:87–89

Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH (2003) Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology 28:916–931

Reay JL, Kennedy DO, Scholey AB (2006) Effects of *Panax ginseng*, consumed with and without glucose, on blood glucose levels and cognitive performance during sustained 'mentally demanding' tasks. J Psychopharmacol 20:771–781

Rogers P, Kainth A, Smit H (2001) A drink of water can improve or impair mental performance depending on small differences in thirst. Appetite 36:57–58

Scholey A, Kennedy D (2004) Cognitive and physiological effects of an "energy drink": an evaluation of the whole drink and of glucose, caffeine and herbal flavouring fractions. Psychopharmacology 176:320–330

Scholey A, Harper S, Kennedy D (2001) Cognitive demand and blood glucose. Physiol Behav 73:585–592

Scholey AB, Sünram-Lea SI, Greer J, Elliott J, Kennedy DO (2009a) Glucose enhancement of memory depends on initial thirst. Appetite 53:426–429

Scholey AB, Sünram-Lea SI, Greer J, Elliott J, Kennedy DO (2009b) Glucose administration prior to a divided attention task improves tracking performance but not word recognition: evidence against differential memory enhancement? Psychopharmacology 202:549–558

Smith A, Kendrick A, Maben A (1992) Effects of breakfast and caffeine on performance and mood in the late morning and after lunch. Neuropsychobiology 26:198–204

Sommerfield AJ, Deary IJ, Frier BM (2004) Acute hyperglycemia alters mood state and impairs cognitive performance in people with type 2 diabetes. Diabetes Care 27:2335–2340

Squire LR (1992) Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. Psychol Rev 99:195–231

Squire L, Zola-Morgan S (1991) The medial temporal lobe memory system. Science 253:1380–1386

Stroop JR (1992) Studies of interference in serial verbal reactions. J Exp Psychol Gen 121:15–23

Sünram-Lea S, Foster J, Durlach P, Perez C (2001) Glucose facilitation of cognitive performance in healthy young adults: examination of the influence of fast-duration, time of day and pre-consumption plasma glucose levels. Psychopharmacology 157:46–54

Sünram-Lea S, Foster J, Durlach P, Perez C (2002a) The effect of retrograde and anterograde glucose administration on memory performance in healthy young adults. Behav Brain Res 134:505–516

Sünram-Lea S, Foster J, Durlach P, Perez C (2002b) Investigation into the significance of task difficulty and divided allocation of resources on the glucose memory facilitation effect. Psychopharmacology 160:387–397

Sünram-Lea S, Foster J, Durlach P, Perez C (2004) The influence of fat co-administration on the glucose memory facilitation effect. Nutr Neurosci 7:21–32

Sünram-Lea S, Owen L, Finnegan Y, Hu H (2010) Dose–response investigation into glucose facilitation of memory performance and mood in healthy young adults. J Psychopharmacol 25:1076–1087

Vanhanen M, Soininen H (1998) Glucose intolerance, cognitive impairment and Alzheimer's disease. Curr Opin Neurol 11:673–677

Winder R, Borrill J (1998) Fuels for memory: the role of oxygen and glucose in memory enhancement. Psychopharmacology 136:349–356