Glucose enhancement of memory is modulated by trait anxiety in healthy adolescent males

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ABSTRACT

Glucose administration is associated with memory enhancement in healthy young individuals under conditions of divided attention at encoding. While the specific neurocognitive mechanisms underlying this 'glucose memory facilitation effect' (GMFE) are currently uncertain, it is thought that individual differences in glucoregulatory efficiency may alter an individual's sensitivity to the GMFE. In the present study, we sought to investigate whether basal hypothalamic-pituitary-adrenal (HPA) axis function (itself a modulator of glucoregulatory efficiency), baseline self-reported stress and trait anxiety influence the GMFE. Adolescent males (age range = 14-17 years) were administered glucose and placebo prior to completing a verbal episodic memory task on two separate testing days in a counter-balanced, within subjects design. Glucose ingestion improved verbal episodic memory performance when memory recall was tested a) within an hour of glucose ingestion and encoding and b) one week subsequent to glucose ingestion and encoding. Basal HPA axis function did not appear to influence the GMFE, however glucose ingestion only improved memory in participants reporting relatively higher trait anxiety. These findings suggest that the GMFE may be mediated by biological mechanisms associated with trait anxiety.

Keywords: episodic memory, glucose, glucoregulation, HPA axis, trait anxiety, adolescents

INTRODUCTION

The ingestion of oral glucose is associated with enhanced performance in a range of cognitive domains, including verbal episodic memory (Foster et al., 1998), working memory (Martin and Benton, 1999), executive functioning (Donohoe and Benton, 1999), reaction time (Owens and Benton, 1994), serial subtraction (Kennedy and Scholey, 2000; Scholey et al., 2001) and attention (Benton et al., 1994). Glucose has only been observed to reliably improve verbal episodic memory performance in healthy young adults when encoding of memory materials takes place under conditions of divided attention (Foster et al., 1998; Sünram-Lea et al., 2001, 2002b). Recent studies from our laboratory suggest that this 'glucose memory facilitation effect' (GMFE) can be extended to healthy adolescent participants (Smith and Foster, 2008a; Smith and Foster, 2008b; Smith et al., in press). It is of interest to further investigate the role of glucose in the mediation of cognitive performance in this age group, given that the basal cerebral metabolic rate of children and adolescents is typically higher than adults (Chiron et al., 1992).

Previous research findings have suggested that individual differences in glucoregulatory efficiency may modulate this enhancing effect of glucose on memory (for reviews see Messier, 2004; Riby and Riby, 2006; Gibson, 2007). However, the direction of the relationship between glucoregulatory efficiency and glucose facilitation of memory remains uncertain, with some studies reporting that a memory benefit is more likely in individuals with poorer glucoregulatory efficiency subsequent to glucose ingestion (Hall et al., 1989; Craft et al., 1994; Messier et al., 1999; Kaplan et al., 2000; Messier et al., 2003), while other studies have reported that individuals exhibiting relatively better glucoregulatory efficiency are more amenable to the GMFE (Craft et al., 1994; Messier et al., 1997; Meikle et al., 2004; Riby et al., 2004; Smith and Foster, 2008a). While age is believed to influence the

relationship between glucoregulatory efficiency and the GMFE (Craft et al., 1994; Smith and Foster, 2008a), the specific mechanisms underlying this relationship are not well understood.

Altered glucoregulatory efficiency has been associated with symptoms of hypothalamic-pituitary-adrenal (HPA) axis dysfunction (Plat et al., 1996; Reynolds et al., 2001; Andrews et al., 2002; Gibson, 2007). HPA activation in response to acute stress leads to the release of cortisol, the primary glucocorticoid hormone in humans. Increased cortisol secretion from the adrenal gland is associated with an elevation in circulating blood glucose concentration (Newton, 2000). Likewise, adrenaline release in response to acute stress, which is subserved by the sympathetic-adrenal medullary (SAM) axis, enables the rapid liberation of glucose in to the bloodstream (Gold, 1995). Endogenous (e.g. Cahill et al., 2003; Smeets et al., 2006; Duncko et al., 2007; Nater et al., 2007), as well as exogenous (e.g. Buchanan and Lovallo, 2001; Lupien et al., 2002; Abercrombie et al., 2003; Kuhlmann and Wolf, 2006) increases in cortisol have been demonstrated to facilitate memory performance, but many factors are known to modulate this relationship, including a) whether the stressor is related to the to-be-remembered stimulus (Joels et al., 2006), b) whether cortisol levels are increased prior to encoding or retrieval (Roozendaal, 2002; Joels et al., 2006), c) the emotionality of the to-be-remembered stimulus (Buchanan and Lovallo, 2001; Jelicic et al., 2004; Payne et al., 2007), and d) the time of day (Het et al., 2005). HPA axis mediation of glucose regulation likely evolved to enable a rapid supply of energy necessary for coping with an acute stressor (Peters et al., 2004). However, HPA axis function can become compromised due to gene/environment interactions involving the presence of glucocorticoid or mineralocorticoid receptor polymorphisms and frequent or prolonged exposure to life stress (de Kloet et al., 2005; DeRijk and de Kloet, 2008). Normal HPA axis functioning is crucial in terms of its role in regulating blood glucose (Peters et al., 2004), rendering individuals predisposed to HPA axis dysfunction at risk for glucoregulatory abnormalities.

On a related note, a number of studies have reported a memory enhancement effect for negative emotionally arousing stimuli (Hamann, 2001). Given that adrenaline cannot cross the blood-brain barrier (Wenk, 1989; Gold, 1995), it has been suggested that stress hormones (including adrenaline and cortisol) may mediate this emotional enhancement effect, at least in part by increasing circulating blood glucose concentration (Brandt et al., 2006). Accordingly, an association has been reported between exposure to emotionally arousing stimuli and elevations in blood glucose concentration (Parent et al., 1999; Blake et al., 2001; Scholey et al., 2006). However, the relationship between blood glucose concentration and emotional memory is complex, given that some studies have reported a) blood glucose increases induced by emotional arousal without memory enhancement (Scholey et al., 2006), and b) superior memory for emotionally laden material independent of blood glucose changes (Gore et al., 2006). Some recent studies have attempted to integrate the findings related to emotional memory and the GMFE by investigating glucose modulation of memory for emotionally arousing stimuli, with extant findings indicating that glucose does not further facilitate memory for such items (Ford et al., 2002; Brandt et al., 2006). This may be due to a 'stress hormone threshold' effect, whereby the level of HPA and/or SAM axis excitation in response to acute stress is too high for the exogenous supply of glucose to be beneficial in terms of neurocognitive enhancement (Brandt et al., 2006). It is therefore of interest to further investigate the neurohormonal mechanisms which may subserve the GMFE, especially in situations where the activation of physiological mechanisms related to stress is too great for additional glucose availability to induce observable influences on memory performance.

Given that a relationship has been demonstrated between glucoregulatory efficiency and HPA axis function, it is postulated here that basal HPA axis function may be one potential mechanism by which glucoregulatory efficiency exerts an influence on the GMFE.

It is therefore of interest to consider experimentally whether individual differences in basal HPA axis function may mediate the GMFE in healthy young individuals. On this basis, the present study aimed to investigate the influence of i) glucoregulatory efficiency, ii) basal HPA axis function and iii) self-ratings of subjective stress and trait anxiety (as subjective indicators of basal stress) on the GMFE. Predicated on previous observations from our laboratory that glucose improves memory only in adolescents exhibiting relatively better glucoregulatory efficiency (Smith and Foster, 2008a), it was hypothesised that verbal episodic memory would be enhanced subsequent to oral glucose ingestion only for those participants exhibiting relatively better glucoregulatory efficiency and 'normal' basal HPA axis function. Further, it was expected that those participants reporting lower levels of stress and trait anxiety would be more amenable to the GMFE. In addition, previous studies have suggested that the GMFE persists when recall is tested 24 hours after treatment and encoding (Manning et al., 1992; Manning et al., 1998b; Sünram-Lea et al., 2002a). A supplementary aim of the present study was to extend these previous findings by investigating whether oral glucose ingestion enhances memory when recall takes place one week post-treatment and encoding.

MATERIALS AND METHODS

Participants

A total of 58 healthy adolescent males, ranging in age between 14 and 17 years (M_{age} = 15.5, SD_{age} = 1.0) participated in the present study. Participants were recruited from secondary schools in Perth, Australia. Three participants reported non-compliance with the fasting instructions of the study. These participants were removed from the data set for all glucose and memory related analyses to avoid any potential confounds from a 'second meal effect'. An additional 15 participants attended only one testing session, and thus were not included in any of the analyses reported here. Therefore, a total of 40 participants were included in the final analyses.

Ethics approval for the present study was obtained from the Human Research Ethics Committee of the University of Western Australia.

Treatment and Design

A within subjects design was employed for the blood glucose analysis, with two within-subjects factors (treatment, time). A within-subjects design was also employed for the primary memory analyses, with a single within-subjects factor (treatment). A subsequent mixed model design also incorporated a single between-subjects factor (glucoregulatory efficiency). Similarly, mixed model designs were also employed to investigate i) baseline self-reported adolescent stress, and ii) trait anxiety, with the former incorporating a single between-subjects factor (stress) and the latter also incorporating a single between-subjects factor (trait anxiety). A further mixed model design also comprised a single between subjects factor (basal cortisol). A between-subjects design with a single between subjects factor (treatment) was used to compare one-week delayed recall forgetting indices between the two treatment conditions.

The glucose treatment consisted of 25 g ‘Glucodin’ Glucose Powder (Boots Healthcare Australia Pty Ltd) dissolved in 300 ml water. The placebo treatment comprised five ‘Equal’ tablets (10% Aspartame, The Merisant Company) dissolved in 300 ml water. It has been reported that this quantity of aspartame is matched in terms of subjective ‘sweetness’ ratings with 25 g glucose powder when dissolved in 300 ml water (Sünram-Lea et al., 2008). Participants attended two test sessions. They were administered one treatment (i.e. glucose or placebo) in the first session and the complementary treatment in the second session. Treatment order was initially counterbalanced, with 29 of the original 58 participants assigned to each treatment order. However, of the 40 participants included in the final analyses, 22 participants consumed the glucose treatment in the first testing session and 18 participants consumed the placebo in the first testing session.

Materials

Saliva Sampling Equipment and Free Cortisol Analysis. Saliva samples were collected using Salivette tubes (Sarstedt Australia, Mawson Lakes, South Australia). Samples were centrifuged at 3,000 rpm for 10 minutes, and stored at -80 degrees Celsius. Awakening salivary free cortisol levels were subsequently quantified in duplicate by a commercially available radioimmunoassay (RIA) kit (DiaSorin, Stillwater, Minnesota, USA) according to the manufacturer’s instructions. All saliva samples were analysed in the same assay to eliminate inter-assay variation. The intra-assay coefficient of variation was 4.63%.

Adolescent Stress Questionnaire (ASQ). The ASQ (Byrne et al., 2007) was developed with Australian adolescents and incorporates 58 items from 10 subscales reflecting various dimensions of adolescent stress. Each item lists a potential stressor, and participants are required to respond on a five-point Likert scale. A score of 1 is indicative of that particular event being perceived as ‘not at all stressful’ (or irrelevant), whereas a score of 5 is indicative

of that particular event being perceived as ‘very stressful’ during the past year. A total score is calculated by summing together the scores for each of the items.

State-Trait Anxiety Inventory (STAI). The STAI (Spielberger, 1983) incorporates two 20-item subscales, measuring a) state anxiety and b) trait anxiety. For the purposes of the present study, only the trait anxiety items of the STAI were administered. The trait anxiety subscale of the STAI requires participants to rate how they ‘generally feel’ with respect to 20 statements on a four-point scale (‘almost never’, ‘sometimes’, ‘often’, ‘almost always’). A score of 4 represents the highest level of anxiety for that item. A total score is calculated by summing together the scores for each of the items.

Modified California Verbal Learning Test-II (CVLT-II). The CVLT-II (Delis et al., 2000) is a test of immediate, short delay and long delay episodic memory for a 16-item supraspan word list. The test comprises a standard form and an alternate form, which can be used for a repeat testing session. The reliability of the alternate form has been demonstrated, with reliability coefficients for immediate, short and long delayed free recall ranging between 0.72 and 0.79 across the different recall phases of the test (Delis et al., 2000; Strauss et al., 2006). In the present study, participants were administered one form in the first session, and the complementary form in the second session, in a counterbalanced order. The order of CVLT-II administration was additionally counterbalanced with treatment order. The modified version of the CVLT-II employed in the present study was extended to a list length of 20 items. The lists comprise five items from each of four semantic categories. The word list was recorded on audiocassette and played five times to the participants, with an immediate free recall trial following each presentation of this list (List A). Immediately subsequent to the fifth immediate free recall trial, an interference list (List B) was played on audiocassette to the participants, followed by an immediate free recall trial for List B items. The CVLT-II additionally comprises free recall phases and cued recall phases (in which participants are

provided with the semantic categories from which the items are drawn, as recall cues) at a short and long delay. A further modification to the CVLT-II that was employed in the present study involved the addition of a one-week delayed free and cued recall phase, in which recall was assessed one-week post-encoding. Details pertaining to the timing of the modified CVLT-II recall phases are included in the Procedure section, below (see also Table 1).

In line with our previous work, participants were required to perform a secondary motor task simultaneously with encoding of the modified CVLT-II word lists in order to increase the difficulty of the memory task by dividing attention across the two tasks (see Sünram-Lea et al., 2002b). Participants were told that performance on the word recall task and hand movement task was equally important, and that they should aim to perform equally well on both tasks. Participants were also told that their hand movements were being recorded by a camcorder, so that the researchers could assess their performance at a later time. The camcorder was used to induce compliance with task instructions to perform both tasks equally well, although no such recording actually took place. Two different motor sequences were performed synchronously with both hands. Participants were required to perform a 'fist' – 'chop' – 'slap' motor sequence in the 2.5 s interval between each of the first five items of the modified CVLT-II. Between each of the next five items of the modified CVLT-II (i.e. items six to ten), participants were required to perform a 'back-slap' – 'chop' – 'fist' motor sequence. Participants were then required to revert back to the first 'fist' – 'chop' – 'slap' sequence between items 11 and 15, and then back to the second 'back-slap' – 'chop' – 'fist' sequence for items 16 to 20. Participants were not informed when to switch from one sequence to the other. They therefore had to keep track of when to switch from one sequence to the next themselves.

Bond-Lader Questionnaire. The modified Bond-Lader scale used here (Bond and Lader, 1974) has also been employed in other studies investigating nutrition, mood and

cognitive functioning (Wesnes et al., 2003; Smith and Foster, 2008a). This instrument requires participants to rate their level of ‘alertness’, ‘contentedness’, ‘calmness’ and ‘satiety’ on 19 bipolar scales. This version of the Bond-Lader scale has been modified from the original via the inclusion of three additional items pertaining to satiety (the original version comprised only alertness, contentedness and calmness factors). The ratings were made by placing a mark at the relevant point on a 100 mm line, with the end of each line reflecting the relevant extremes of the dimension being rated (e.g. ‘alert’ versus ‘drowsy’). A higher score indicates a higher level of the relevant dimension.

Blood Glucose Equipment. Blood glucose concentration was measured using a MediSense Optium Blood Glucose Meter, MediSense Optium Point-of Care Disposable Blood Glucose Test Strips and a MediSense Auto-Lancing Device with thin lancets (Abbott Diagnostics Division, Doncaster, Victoria, Australia). One drop of capillary blood was obtained from the fingertip of each participant for each measurement of blood glucose using the lancing device. The inter-assay variation for this sampling procedure ranges by no more than 2.9% to 5.1% (according to manufacturer’s user guide). The validity of this procedure has also been demonstrated by the manufacturer ($r = 0.96 - 0.98$ between this method and the laboratory reference method).

Procedure

Approximately one week prior to the first testing session, written informed consent was obtained from participants and their parents. At this time, participants were provided with three Salivette tubes, and were asked to obtain a saliva sample, 10 minutes post-awakening on three separate mornings before the first testing session by chewing on the Salivette cotton roll for three minutes. Participants were told not to consume any food or drinks prior to collecting the samples. They were also asked to take the samples only on days

at which they woke up at their typical time of awakening (i.e. to avoid collecting the samples on days when they woke considerably earlier or later than the time that they would normally wake up on a typical school day). Participants were required to record the time at which each sample was taken. Samples collected outside of the 5-30 minute post-awakening window were excluded from that participant's basal cortisol average. Further, participants were also given a copy of the STAI and ASQ at this time, for completion prior to the first testing session.

Participants subsequently attended two testing sessions. They were instructed not to consume any food or drink, other than water, from 10:30 pm on the evening prior to each of these testing sessions. All test sessions began between 7:30 and 9:00 am. Participants first completed the modified Bond-Lader questionnaire, and baseline blood glucose concentrations were measured. Immediately following the measurement of blood glucose concentrations, participants consumed one of the two treatments. Participants were blind as to the contents of the drinks, and were told only that they comprised a "sweet tasting liquid". Participants were allowed 10 minutes to consume their designated treatment. Ten minutes following the completion of treatment consumption, blood glucose concentrations were measured and participants were administered the modified Bond-Lader questionnaire for the second time. Participants then completed the immediate free-recall trials of the modified CVLT-II (List A, trials 1-5), followed by the modified CVLT-II interference word list (List B). Motor sequences were performed during encoding of each CVLT-II list. Participants were subsequently administered the third modified Bond-Lader questionnaire, and a third measurement of blood glucose concentration was obtained. Following this, participants completed the short delay recall phases of the CVLT-II. Following a short break (10 minutes), the final measurements of blood glucose concentrations were recorded, and the

final administration of the modified Bond-Lader questionnaire was given. The long delay recall phases of the CVLT-II were then completed.

A second testing session was conducted exactly one week after the first testing session. The second testing session was identical to the first testing session, except that the testing procedure was preceded by a free recall and a cued recall test of the memory items from the first testing session. This one-week delayed recall phase was a between-subjects comparison, with the treatment administered in the first testing session (glucose or placebo) determining whether participants were assigned to the glucose or placebo treatment groups for the purposes of statistical analysis. On the second testing occasion, participants were also administered the complementary treatment (glucose or placebo) and the complementary version of the modified CVLT-II (standard form or alternate form) to that administered in the first testing session. For details of the precise timings of each of the events within the study protocol, see Table 1.

INSERT TABLE 1 ABOUT HERE

Statistical Analysis

Pearson correlation analyses were employed to investigate the relationship between mean awakening salivary free cortisol level, ASQ scores and trait anxiety scores.

A treatment (glucose, placebo) x time (-10, 10, 40, 60) repeated measures analysis of variance (ANOVA) was used to analyse blood glucose data. Likewise, Bond-Lader scores were also investigated with a treatment (glucose, placebo) x time (-10, 10, 40, 60) repeated measures ANOVA.

In terms of the memory analyses, a treatment (glucose, placebo) x trial (1, 2, 3, 4, 5) repeated measures ANOVA was employed to analyse the immediate free recall data. Delayed

recall analyses (short delay free recall, short delay cued recall, long delay free recall, long delay cued recall) were conducted using repeated measures ANOVAs with treatment (glucose, placebo) as a single repeated measures factor.

Further, one-week delayed recall forgetting indices were calculated by subtracting the number of items recalled in the one-week delayed free recall phase from the long delay free recall phase in the first testing session (free recall), and by subtracting the number of items recalled in the one-week delayed cued recall phase from the long delay cued recall phase in the first testing session (cued recall). These calculations yielded scores that reflect the total number of items 'forgotten' in the one week-interval between the first and second testing session for each individual. One-week delayed recall forgetting indices were analysed for both free and cued recall with a one-way ANOVA, with treatment (glucose, placebo) as a single between subjects factor.

A group of relatively 'better glucoregulators' and a group of relatively 'poorer glucoregulators' was established by calculating the area under the glucose response curve (AUC) for each participant on the glucose testing day (for the formula used in this calculation see Smith and Foster, 2008a; see also Sünram-Lea et al., 2008), and performing a median split on these values (with a higher score indicating poorer glucoregulatory efficiency; better ≤ 60, poorer ≥ 60.5). The combined influence of treatment and glucoregulatory efficiency on the memory outcomes was analysed using a treatment (glucose, placebo) x glucoregulatory efficiency (better, poorer) mixed model ANOVA, with repeated measures on the treatment factor.

In order to investigate the influence of basal HPA axis function on the memory outcomes, participants were stratified into three groups on the basis of mean awakening salivary free cortisol (low, normal, high). These groups were formed by comparing awakening free cortisol values against those of a reference sample of 723 adolescents aged

between 16.0 and 18.4 years (*M*=17.1 years) enrolled in the Western Australian Pregnancy Cohort (Raine) Study (for details of this cohort see Newnham et al., 1993; Newnham et al., 2004; Robinson et al., 2008). It is considered appropriate to compare the cortisol values of the present study against this reference sample, given that the reference sample live in the same area, are similar in age to the present study sample and have their awakening salivary free cortisol values quantified using the same methodological approach. Participants exhibiting a mean awakening free cortisol value between the 40^{th} and 60^{th} percentile when compared to this reference group (mean awakening salivary free cortisol range = 0.80-0.96 μg/dl) were considered to exhibit awakening free cortisol values within the normal range. Individuals exhibiting values lower or higher than this range were considered to fall into the 'low' or 'high' awakening free cortisol groups respectively. Assigning participants to three groups in this manner is more appropriate than using median splits, as the method used in the present study enables the consideration of individuals within the normal range of awakening salivary free cortisol levels, as well as those individuals who fall either side of the normal range to be considered independently. The combined influence of treatment and basal HPA axis function on the memory outcomes was analysed using a treatment (glucose, placebo) x awakening free cortisol (low, normal, high) mixed model ANOVA, with repeated measures on the treatment factor.

A group of individuals reporting relatively lower baseline stress and a group of individuals reporting relatively higher baseline stress were established for analysis by performing a median split on the total ASQ scores (low ≤ 126; high ≥ 129). Likewise, a group of adolescents reporting relatively lower trait anxiety and a group with relatively higher trait anxiety was established by performing a median split on the trait anxiety scores (low ≤ 19; high ≥ 20). The combined influence of treatment and baseline stress on the memory outcomes was analysed using a treatment (glucose, placebo) x stress (low, high)

mixed model ANOVA, with repeated measures on the treatment factor. Similarly, a treatment (glucose, placebo) x trait anxiety (low, high) mixed model ANOVA with repeated measures on the treatment factor, was employed to investigate the influence of treatment and trait anxiety on the memory outcomes.

RESULTS

Basal HPA Axis Function

The mean of the awakening salivary cortisol values was calculated for each participant as a measure of basal HPA axis function. Mean awakening free cortisol values ranged between 0.45 μg/ dl and 2.68 μg/ dl within the present study sample. Correlation analyses between the mean awakening cortisol level, self-reported stress and trait anxiety revealed a significant positive relationship between self-reported stress and trait anxiety (r = -0.58, p = <.001). The negative relationship between trait anxiety and awakening cortisol approached significance (r = -0.26, p = .06). Awakening cortisol and baseline stress were not significantly correlated.

INSERT TABLE 1 ABOUT HERE

Blood Glucose Concentration

A significant treatment x time interaction effect was observed, $F(3, 37) = 29.13$, $p < .001$, with a large effect size (partial $\eta^2 = .70$). Planned comparisons revealed that, as anticipated, blood glucose concentrations were significantly higher for the glucose condition, relative to the placebo condition, 10 minutes, $t(39) = 4.76$, $p < .001$, 40 minutes, $t(39) = 8.98$, $p < .001$, and 60 minutes, $t(39) = 4.48$, $p < .001$, post-treatment delivery. Blood glucose concentrations between the glucose and placebo conditions did not differ at baseline, $t(39) = 0.59$, *n.s.* (see Figure 1).

INSERT FIGURE 1 ABOUT HERE

Bond-Lader Scale

Time x treatment interactions failed to reach significance on the alertness, contentedness, calmness and satiety subscales of the Bond-Lader questionnaire.

Modified CVLT-II

In order to interpret data in a meaningful manner, participants who performed at ceiling (i.e. recalled 100% of the to-be remembered items) in either the glucose or placebo treatment condition on any given recall phase of the CVLT-II were excluded from the analyses for that recall phase.

Immediate Free Recall. A significant treatment x trial interaction effect was observed $F(4, 28) = 3.09$, $p < .05$, with a moderate effect size (partial $\eta^2 = .31$). Planned comparisons revealed that a significantly greater number of items was recalled subsequent to glucose ingestion, relative to placebo ingestion, on the fourth trial, $t(31) = 2.29$, $p < .05$, and fifth trial, $t(31) = 2.80$, $p < .01$, of the immediate free recall phase (see Figure 2).

INSERT FIGURE 2 ABOUT HERE

Delayed Recall. A significantly greater number of items was recalled subsequent to glucose ingestion, relative to placebo ingestion on the short delay free recall, $F(1, 33) = 5.23$, $p < .05$, long delay free recall, $F(1, 31) = 5.85$, $p < .05$, and long delay cued recall, $F(1, 32) = 5.40$, $p < .05$, phases of the CVLT-II (see Table 2).

In terms of the one-week delayed recall data, participants who performed at ceiling in either recall phase used to determine the forgetting indices (long delay free recall or one-week delayed recall) were removed from the forgetting index analyses, analogously to the aforementioned CVLT analyses. This yielded a sample size of 35 for the one-week free recall analyses (19 in the glucose group, 16 in the placebo group) and a sample size of 34 for the

one-week cued recall analyses (18 in the glucose group, 16 in the placebo group). A between-subjects comparison revealed a trend toward significantly greater forgetting in the placebo treatment group relative to the glucose treatment group on one-week delayed free recall, $F(1, 33) = 3.86$, $p = .06$, but not for cued recall (see Figure 3).

INSERT TABLE 2 AND INSERT FIGURE 3 ABOUT HERE

Glucose Regulation. The treatment x glucoregulatory efficiency interaction was nonsignificant for all recall phases of the CVLT-II.

Basal HPA Axis Function. Treatment x awakening free cortisol interactions were nonsignificant for all recall phases of the modified CVLT-II.

ASQ and Trait Anxiety. The treatment x stress interaction was nonsignificant for all recall phases of the CVLT. However, a significant treatment x trait anxiety interaction effect was observed on short delay free recall, $F(1, 32) = 4.16$, $p = .05$, and on long delay cued recall, $F(1, 31) = 4.37$, $p < .05$. Post hoc Bonferroni adjusted pairwise t-tests revealed that for short delay free recall, memory performance was significantly better in the glucose condition relative to the placebo condition only for those participants with relatively higher self-reported trait anxiety, $t(17) = 3.19$, $p < .05$. Likewise, for long delay cued recall, post-hoc Bonferroni adjusted pairwise t-tests revealed that memory performance was significantly better in the glucose condition relative to the placebo condition only for those participants with relatively higher self-reported trait anxiety, $t(17) = 3.41$, $p = .01$ (see Table 3).

INSERT TABLE 3 ABOUT HERE

DISCUSSION

The present study aimed to replicate previous work from our laboratory which suggests that the ingestion of oral glucose facilitates verbal episodic memory in healthy adolescents under conditions of divided attention at encoding (Smith and Foster, 2008a). Further, the hypothesis that individual differences in basal HPA axis function, self-reported stress and trait anxiety modulates the GMFE was investigated in the present study. Healthy adolescent males completed self-report measures of adolescent stress and trait anxiety. Awakening salivary free cortisol was also measured on up to three different mornings prior to memory testing. Participants presented for memory testing on two different occasions subsequent to an overnight fast. Encoding of memory test materials took place simultaneously with a secondary motor task, which was preceded by ingestion of either a glucose or placebo control solution. As anticipated, blood glucose concentration was significantly elevated subsequent to glucose ingestion for the glucose condition, relative to the placebo condition.

In accordance with previous findings concerning the GMFE, participants exhibited superior performance on the short delay free recall, long delay free recall and long delay cued recall phases of the modified version of the CVLT-II subsequent to ingestion of the glucose treatment relative to placebo. The rate of learning was also shown to be faster in the glucose condition relative to placebo, with participants demonstrating significantly enhanced performance on the fourth and fifth trials of the immediate free recall phase of the modified CVLT-II subsequent to glucose ingestion. Further, the present study findings suggest that the facilitatory influence of glucose on memory encoding can be observed one week post-encoding, on the basis of the one-week free recall test in which more items were forgotten when the placebo had been administered prior to encoding, relative to glucose. Scores on the Bond-Lader scale did not differ significantly between the two treatment conditions, implying

that the observed treatment effects on memory were not influenced by fluctuations in mood or satiety across the testing sessions. This is despite a recent finding by Scholey and colleagues (Scholey et al., 2009) which reported an increase in self ratings of hunger subsequent to ingestion of a placebo drink relative to a glucose treatment. However, in this previous study, ingestion of the placebo drink was associated with increased hunger only under single-, but not dual-task conditions (Scholey et al., 2009).

The finding that glucose ingestion prior to encoding enhanced memory when retrieval took place one week later is in line with previous reports that glucose improves memory when glucose administration and encoding take place 24 hours prior to retrieval (Manning et al., 1992; Manning et al., 1998b; Sünram-Lea et al., 2002a). Such findings support the notion that glucose enhances memory encoding and/ or consolidation, rather than retrieval, as under these conditions glucose would have been cleared from the bloodstream by the time of memory retrieval. The one week delayed recall finding of the present study extends these previous study results (Manning et al., 1992; Manning et al., 1998b; Sünram-Lea et al., 2002a) by a) suggesting that the effect of glucose on memory encoding lasts at least one week, and b) demonstrating that the effect of glucose on 'extra-long' delayed recall can be generalised to healthy adolescents. It is of further interest that the observed trend towards significantly reduced forgetting in the glucose condition, relative to the placebo condition was evident only for free recall and did not extend to cued recall. It can perhaps be inferred, on the basis of this finding, that the recall cues provided to the participants during the one week cued recall phase triggered a memory benefit that could not be further facilitated by pre-encoding glucose administration. This finding may also be related to the notion that the GFME is associated with more effortful cognitive processing, as free recall was likely to have been more cognitively demanding for the participants than cued recall.

In contrast to our previously reported finding that the GMFE is mediated by glucoregulatory efficiency in adolescents (Smith and Foster, 2008a), individual differences in glucoregulatory efficiency were not found to influence the enhancement effect of glucose on memory observed here. Further, individual differences in awakening salivary free cortisol and self-reported stress were not observed to influence the glucose enhancement effect in the present study. However, trait anxiety was found to mediate the effect of glucose on short delay free recall and long delay cued recall performance; for these two CVLT recall phases a glucose enhancement effect was observed only for those participants who reported relatively higher trait anxiety. While it is unlikely that this finding was mediated by the HPA axis, it is nevertheless of interest to discuss further the role of trait anxiety as a possible mediator of the glucose memory facilitation effect.

To our knowledge, the present study represents the first report that the GMFE is influenced by trait anxiety. Given that negative affective states are associated with memory impairment (McEwen and Sapolsky, 1995; Sala et al., 2004), this finding may be considered in line with previous reports that individuals who are not able to perform at their cognitive peak, such as clinical populations with memory deficits (Manning et al., 1998a; Pettersen and Skelton, 2000; Watson and Craft, 2004; Stone and Seidman, 2008) and healthy elderly individuals (Craft et al., 1994; Riby et al., 2004) are most sensitive to glucose enhancement of memory. The finding that individuals with relatively higher trait anxiety are most amenable to the GMFE would appear to have important implications for the body of research which has demonstrated a memory advantage for negative emotionally arousing stimuli (see Hamann, 2001), especially if endogenous blood glucose increases mediate this effect (Gold, 1995). Although speculative, it may well be that individuals reporting high trait anxiety are relatively more sensitive to emotionally arousing stimuli, and therefore exhibit relatively better memory for such items. This suggestion should be investigated further in future

studies. Likewise, the possible neurohormonal interactions underlying the relationship between trait anxiety, blood glucose increases and memory warrant further investigation. However, it appears unlikely that resting HPA axis activity is involved in subserving this relationship given the negative correlation between awakening salivary cortisol and trait anxiety observed in the present study. With respect to the extant literature, the relationship between trait anxiety and HPA axis function remains somewhat uncertain, however it has been reported that trait anxiety mediates the cortisol response to stress (Schlotz et al., 2006). Nevertheless, it is likely that the observed trait anxiety findings of the present study are subserved by a physiological mechanism, perhaps related to the SAM axis. It would therefore be of interest to investigate in future studies whether basal SAM function modulates the GMFE, although it is difficult to obtain robust biomarkers underlying basal SAM axis function.

As mentioned above, glucoregulatory efficiency was not observed to mediate the GMFE in the present study. Other researchers have reported that healthy young individuals with relatively poor glucoregulatory efficiency are more amenable to the GMFE (Craft et al., 1994). This finding (Craft et al., 1994) is in line with the aforementioned notion that glucose enhancement of memory is most reliably observed in individuals who are not performing at their cognitive peak (given that poor glucoregulatory efficiency is associated with relatively poorer memory, Awad et al., 2002; Lamport et al., 2009). Nevertheless, as previously noted, there are some inconsistencies between studies regarding the direction of the relationship between glucoregulatory efficiency and glucose enhancement of memory. Specifically, it has been suggested that the influence of glucoregulatory efficiency on the GMFE is dependent on age, with Craft and colleagues (1994) reporting that glucose enhances memory in older individuals with relatively better glucoregulatory efficiency but in younger individuals with relatively poorer glucoregulatory efficiency. However, this framework is inconsistent with

the findings of a previous study from our laboratory in which the GMFE was observed only in adolescents exhibiting relatively better glucoregulatory efficiency (Smith and Foster, 2008a). This discrepancy may be explained by the fact that the method typically employed to determine glucoregulatory efficiency is to perform a median split on some measure of glucose response. Due to the relatively small sample size of most studies in this area, the definition of 'good' and 'poor' glucose regulation can vary drastically between studies due to this method of establishing groups on the basis of glucoregulatory efficiency. We have suggested previously that given the inverted-U shaped dose-response curve purported to underlie the GFME (Parsons and Gold, 1992), this disparity between studies in defining 'good' versus 'poor' glucose regulation may lead to variation between studies with regard to whether the blood glucose concentration of the 'poorer glucoregulators' or 'better glucoregulators' (as defined by the individual studies) is within the optimal range to induce a memory improvement (Smith and Foster, 2008a). The role of glucoregulatory efficiency in mediating the GMFE merits further attention in future research investigations. This is a particularly important consideration in the context of better understanding the mechanisms underlying the GMFE, especially in situations in which proposed mechanisms (such as HPA axis function in this case) are influenced by glucoregulatory efficiency.

It was hypothesised prior to the present study that basal HPA axis function would modulate the glucose enhancement effect, predicated by the established relationship between glucoregulatory efficiency and HPA axis function (Plat et al., 1996; Reynolds et al., 2001; Andrews et al., 2002; Gibson, 2007). However, as mentioned above, the findings of the present study indicated that glucoregulatory efficiency, measured by calculating the AUC for each participant, did not influence the GMFE. In this context, it is perhaps unsurprising that awakening salivary free cortisol was not observed to modulate the effect of glucose on memory in the present study. This may in part be due to the fact that the adolescent

participants who took part in the present study represent a relatively healthy sample of individuals. In order to comprehensively address this question in future studies, it would be of interest to include more participants who exhibit glucoregulatory and/or HPA axis profiles outside of the normal range.

In summary, the present study supported previous work from our laboratory that glucose can facilitate memory in healthy adolescents (Smith and Foster, 2008a; Smith and Foster, 2008b). Under conditions of divided attention, glucose ingestion was observed to enhance the rate of learning and delayed recall of a supraspan word list. Neither glucoregulatory efficiency nor basal HPA axis function were found to modulate the GMFE. However, individual differences in trait anxiety were observed to influence the enhancement effect of glucose on memory. These findings offer further support to the notion that glucose facilitation of memory is most reliably observed in individuals who are not able to perform at their cognitive peak, and suggest that the biological mechanisms underlying trait anxiety may modulate the GMFE.

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Table 1

The study procedure (the time in minutes of each procedure prior/subsequent to treatment delivery is displayed in the left column).

t (mins)	Procedure
-15	One-week delayed recall (second testing session only)
-10	First blood glucose measurement
	First modified Bond-Lader scale
0	Treatment administration
10	Second blood glucose measurement
	Second modified Bond-Lader scale
20	CVLT-II Immediate free recall trials with secondary motor task
40	Third blood glucose measurement
	Third modified Bond-Lader scale
50	CVLT-II Short delay recall
60	Fourth blood glucose measurement
	Fourth modified Bond-Lader scale
70	CVLT-II Long delay recall

Table 2

CVLT-II delayed recall results for the glucose and placebo conditions. Mean values are displayed, with standard deviations in parentheses. Repeated measures ANOVA revealed a significant difference in the total number of items recalled between the glucose and placebo conditions for the short delay free recall, long delay free recall and long delay cued recall phases.

Modified CVLT-II recall phase	Glucose	Placebo	*p*	*N*
Short delay free recall	14.0 (3.3)	12.7 (4.6)	< .05	34
Short delay cued recall	14.2 (3.0)	13.9 (4.4)	0.65	34
Long delay free recall	14.4 (3.2)	13.3 (4.4)	< .05	32
Long delay cued recall	14.8 (3.2)	13.7 (4.4)	< .05	33

Table 3

CVLT-II delayed recall results for the glucose and placebo conditions, arranged by relative trait anxiety. Mixed model ANOVAs and Bonferroni adjusted post-hoc pairwise t-tests revealed a significant difference between the number of items recalled in the glucose and placebo treatment conditions only for those participants reporting relatively higher trait anxiety, at the short delay free recall and long delay cued recall phases.

	Low Trait Anxiety			High Trait Anxiety		
Modified CVLT-II recall phase	Glucose	Placebo	*p*	Glucose	Placebo	*p*
Short delay free recall*	14.1 (3.6)	14.0 (4.7)	*n.s.*	13.8 (3.2)	11.5 (4.4)	< .05
Short delay cued recall	14.1 (3.2)	14.8 (3.9)	-	14.2 (3.0)	13.2 (4.7)	-
Long delay free recall	15.0 (3.4)	14.6 (4.3)	-	13.9 (3.2)	12.3 (4.3)	-
Long delay cued recall*	15.0 (3.5)	14.9 (4.2)	*n.s.*	14.6 (3.1)	12.7 (4.4	.01

Treatment x Trait Anxiety Interactions: *$p \leq 0.05$

Figure Captions

Figure 1

Blood glucose concentrations (mean ± SE) for the glucose and placebo treatment conditions at each measurement time point (*N*=40). Repeated measures ANOVA and planned comparisons revealed that blood glucose concentration was higher for the glucose condition, relative to the placebo condition at the 10 minute, 40 minute and 60 minute post-treatment time points.

Figure 2

Total items recalled (mean ± SE) on trials 1-5 of the Immediate Free Recall phase of the CVLT-II. Repeated measures ANOVA and planned comparisons revealed that a significantly greater number of items was recalled subsequent to glucose ingestion, relative to placebo ingestion, on trial 4 and trial 5 (*N*=32).

Figure 3

Total items forgotten (mean ± SE) between the Long Delay Recall phase in the first testing session, and the one-week delayed recall phase of the second testing session for the glucose and placebo treatment conditions (i.e. the treatment administered in the first testing session). One-way ANOVA revealed a trend toward greater ‘forgetting’ in the free recall phase for the placebo condition, relative to the glucose condition, one-week post-encoding.

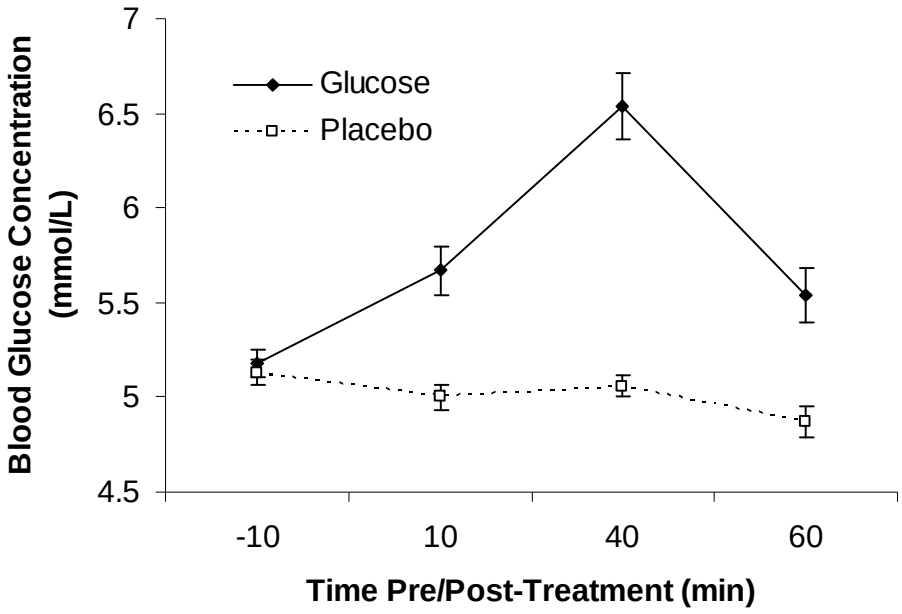
Blood Glucose Concentration (mmol/L)
7
6.5
6
5.5
5
4.5
Glucose
Placebo
-10
10
40
60
Time Pre/Post-Treatment (min)

Figure 1

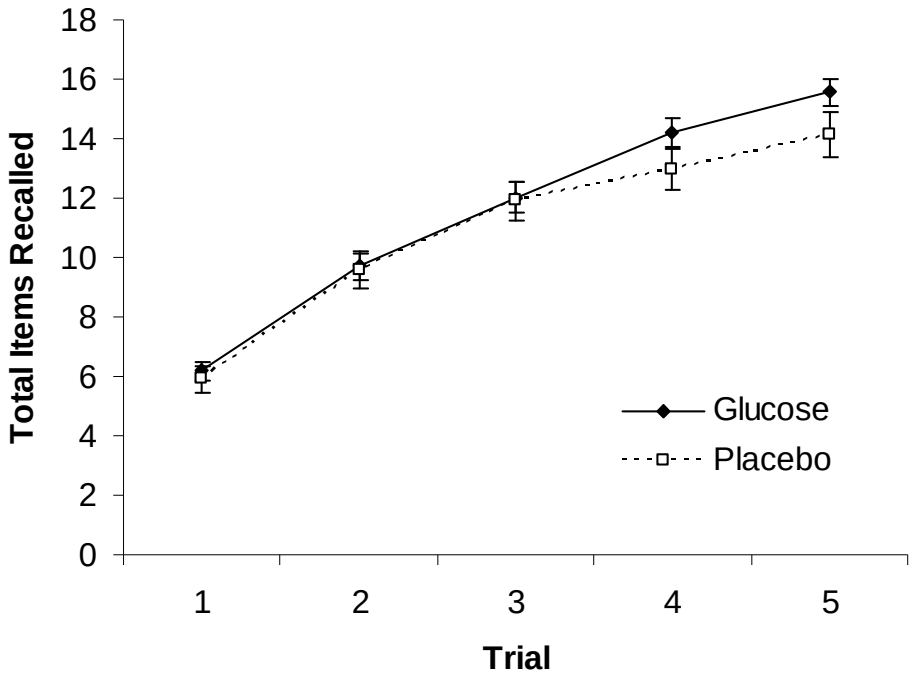
Total Items Recalled
18
16
14
12
10
8
6
4
2
0
1
2
3
4
5
Trial
Glucose
Placebo

Figure 2

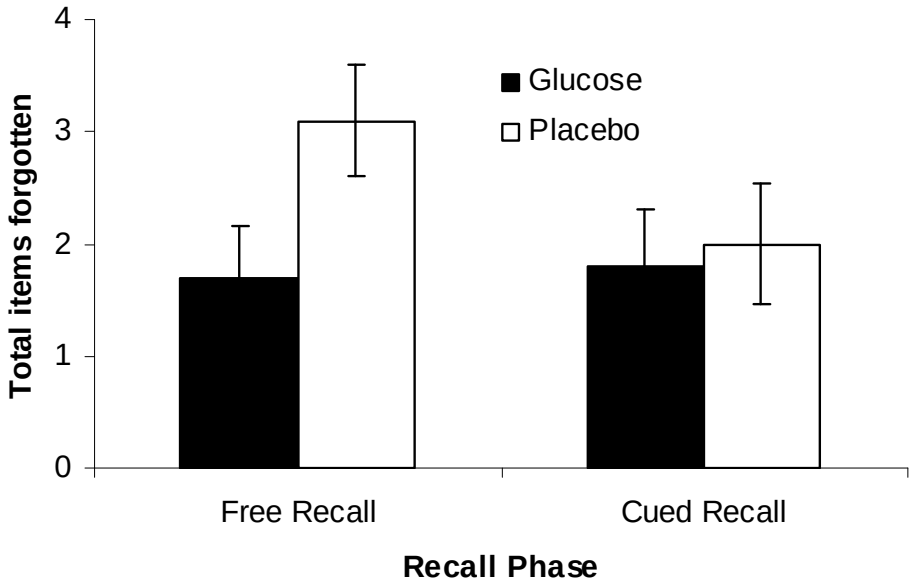
4
3
2
1
0
Total items forgotten
Glucose
Placebo
Free Recall
Cued Recall
Recall Phase

Figure 3