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**Glucoregulatory and order effects on verbal episodic memory in healthy
adolescents after oral glucose administration**

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Abstract

The ingestion of oral glucose has been observed to facilitate memory performance in both elderly individuals and in young adults. However, fewer studies have investigated the effect of glucose on memory in children or adolescents. In the present study, the ingestion of a glucose laden drink was observed to enhance verbal episodic memory performance in healthy adolescents under conditions of divided attention, relative to a placebo drink. Further analyses found that this glucose memory facilitation effect was observed only in adolescents exhibiting better glucoregulatory efficiency. These findings demonstrate that the glucose memory facilitation effect can be generalised to younger individuals. The importance of controlling for treatment order in within-subjects designs investigating the glucose memory enhancement effect is also discussed.

The brain relies upon glucose as its primary fuel (Sieber & Traystman, 1992). In recent years, a rich literature has developed from both human and animal studies indicating that increases in circulating blood glucose can facilitate cognitive functioning (for a review see Messier, 2004). This phenomenon has been termed the ‘glucose memory facilitation effect’ (Foster, Lidder, & Sünram, 1998). It has been suggested that older individuals may benefit to a greater degree from glucose administration, as healthy young individuals are close to their ‘cognitive peak’ (Foster et al., 1998). However, glucose has also been observed to facilitate memory in healthy young adults (e.g. Benton, Owens, & Parker, 1994; Foster et al., 1998; Sünram-Lea, Foster, Durlach, & Perez, 2001; Meikle, Riby, & Stollery, 2005). A meta-analytic review of the glucose memory facilitation effect has supported the view that verbal episodic memory is the cognitive domain that is most amenable to improvement subsequent to glucose ingestion (Riby, 2004).

While an abundant literature now exists suggesting that glucose ingestion can facilitate verbal episodic memory in healthy young adults, it has also been suggested that glucose only reliably facilitates memory in this group of individuals under conditions of divided attention at encoding (Sünram-Lea, Foster, Durlach, & Perez, 2002). Sünram-Lea and colleagues (2002) administered either a glucose or a placebo drink to healthy young adult participants, before presenting them with a list of to-be-remembered words under one of four ‘divided attention’ conditions. Glucose was observed to facilitate memory recall, relative to placebo, when participants performed a secondary motor task or key tapping task concurrently with word list encoding. However, the authors failed to observe the glucose memory facilitation effect when participants were not required to perform a secondary task, or when cognitive demand

was increased by asking participants to recall a longer word list, with target items differentiated by the speaker's gender..

By contrast, other researchers have observed that manipulating cognitive load, but not divided attention can induce a glucose memory facilitation effect in healthy young adults. For example, glucose has been demonstrated to enhance performance in these individuals on a difficult serial subtraction task, but not on a serial subtraction task associated with a relatively lower cognitive load (Kennedy & Scholey, 2000; Scholey, Harper, & Kennedy, 2001). In addition, Meikle, Riby and Stollery (2005) have reported that glucose facilitation of verbal episodic memory for serial position is more reliably observed in younger adults when target lists are longer.

It has been further suggested that individual differences in peripheral glucose regulation may alter an individual's sensitivity to glucose enhancement of memory. Glucose regulation is reflected by the phenomenon whereby blood glucose concentration rises for approximately 30 minutes subsequent to a glucose load, followed by a return to baseline blood glucose concentration - typically within approximately two hours (Donohoe & Benton, 2000). A link between glucoregulatory efficiency and cognitive functioning has now been well established (Wenk, 1989; Awad, Gagnon, Desrochers, Tsiakas, & Messier, 2002; Messier, 2005). More specifically, it has been reported that glucose cognitive enhancement effects are most profound in older adults with poorer glucose regulation (Hall, Gonder-Frederick, Chewning, Silvera, & Gold, 1989; Kaplan, Greenwood, Winocur, & Wolever, 2000; Messier, Tsiakas, Gagnon, Desrochers, & Awad, 2003). These findings have also been replicated in younger individuals: young adult males with poor glucose regulation have also been observed to demonstrate superior paragraph recall subsequent to glucose ingestion, relative to ingestion of a saccharin control drink

(Craft, Murphy, & Wemstrom, 1994). In addition, younger individuals with poor glucose regulation have been shown to exhibit inferior performance on a verbal episodic memory task relative to better glucoregulators - an effect that is ameliorated if glucose is consumed prior to memory encoding (Messier, Desrochers, & Gagnon, 1999). It has been theorised that glucose ingestion is most likely to facilitate memory in younger individuals exhibiting poor glucose regulation, as only in such individuals does blood glucose concentration remain elevated for a sufficient time period to exert a memory enhancing effect (Craft et al., 1994). By contrast, it has been reported that, in older adults, the glucose memory facilitation effect is more pronounced in those individuals exhibiting relatively better glucose regulation (Craft et al., 1994; Messier, Gagnon, & Knott, 1997; Meikle, Riby, & Stollery, 2004; Riby, Meikle, & Glover, 2004).

While the effect of glucose on memory has been well investigated in younger and older adults, fewer studies have investigated glucose effects on memory in children and adolescents. Lapp (1981), reported that subsequent to ingestion of a carbohydrate rich meal (which elevated blood glucose concentration), healthy adolescents outperformed a fasted control group of adolescents on a paired-associate learning task. The findings of Lapp's (1981) study may, however, reflect the negative effects of fasting on memory, rather than the positive effects of elevated blood glucose (see Doniger, Simon, & Zivotofsky, 2006). It has also been reported that attentional capacity benefits from ingestion of a confectionary snack in school children (Busch, Taylor, Kanarek, & Holocomb, 2002). Further, the consumption of breakfast has been associated with superior attention and memory in children (Wesnes, Pincock, Richardson, Helm, & Hails, 2003), an effect that is more apparent subsequent to the ingestion of breakfast meals associated with a slower and more

prolonged release of glucose into the bloodstream (Mahoney, Taylor, Kanarek, & Samuel, 2005; Ingwersen, Defeyter, Kennedy, Wesnes, & Scholey, 2007). However, the macronutrient composition of the different treatments used in these studies renders it difficult to infer whether glucose, or other potentially cognitive enhancing nutritional components of these treatments (Gibson & Green, 2002), were responsible for the findings.

Therefore, the effect of pure glucose ingestion on episodic memory in healthy adolescents has not been well established. Adolescence is a unique period with regard to brain development (Giedd, Blumenthal, Jeffries, Castellanos, Liu, Zijdenbos et al., 1999), and also a time of increased vulnerability for experiencing heightened stress (Byrne, Davenport, & Mazanov, 2007). This is relevant, given that stress hormones (i.e. cortisol) are known to impact upon glucose regulation (Plat, Byrne, Sturis, Polonsky, Mockel, Fery et al., 1996). While the measurement of stress hormone levels is beyond the scope of the present investigation, it is nevertheless important to establish whether glucose ingestion has a similar effect on memory in this age group compared with other populations in which the glucose memory facilitation effect has been demonstrated.

The aim of the present study was therefore to investigate the influence of glucose ingestion and glucoregulatory efficiency on verbal episodic memory in healthy adolescents. In line with previous research conducted with healthy young adults, memory encoding took place under dual task conditions (Foster et al., 1998; Sünram-Lea et al., 2001, 2002). It was hypothesised that oral glucose ingestion would enhance memory for a supraspan word list in healthy adolescents, relative to a sweetness matched placebo. It was further hypothesised that the glucose memory facilitation effect would be observed only in the healthy adolescent participants with

poor glucose regulation, in accordance with previous findings indicating that glucose facilitation of memory is observed only in young adults with poor glucose regulation (Craft et al., 1994; Messier et al., 1999).

Method

Participants

A total of 32 healthy adolescents participated in the present study (12 males, 20 females), ranging in age between 14 and 17 years ($M_{\text{age}} = 15.6$, $SD_{\text{age}} = 0.9$). Participants were recruited from independent and government secondary schools in Perth, Western Australia. One participant withdrew from the study after becoming nauseous subsequent to consumption of the glucose drink. A further five participants attended only one testing session, and thus were not included in any of the analyses reported here. An additional participant reported being non-compliant with the fasting instructions of the study. This participant was also removed from the data set for all analyses in order to avoid any potential confounds from a ‘second meal effect’. Therefore, a total of 25 participants were included in the final analyses.

Prior to testing, all participants and parents of participants were provided with a questionnaire in order to screen for the following exclusion criteria:

- Diagnosis of diabetes mellitus and / or a history of hypoglycaemic or hyperglycaemic episodes,
- Lactose intolerance,
- Allergies to foods administered as part of the experimental procedure,
- Diagnosis of phenylketonuria (PKU),
- Needle / blood phobia or objection to having blood samples taken (e.g. for religious or cultural reasons),

- Diagnosis of an eating disorder, or
- Having sought medical advice for a weight control issue.

This questionnaire has been used to screen for exclusion criteria in other investigations of nutritional influences on psychological functioning in our laboratory (e.g. Foster, Smith, Woodman, Zombor, & Ashton, 2007). A 'yes' response by the participant or their parent to any of the exclusion criteria listed above renders that participant ineligible to participate in the study. Based on both parental and participant responses to the screening questionnaire, all remaining 25 participants were eligible to participate in the study.

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. There was a single within participants factor (treatment), with two levels (glucose, placebo). A subsequent mixed model design also incorporated a single between subjects factor (treatment order), with two levels (glucose first, placebo first).

In order to analyse whether individual differences in glucose regulation impacted upon the glucose memory facilitation effect, a median split was performed on the data for the area under the glucose response curve (AUC) for each participant. The above mixed model analysis was then repeated i) for individuals demonstrating relatively better glucose regulation and ii) for individuals demonstrating relatively poorer glucose regulation.

The glucose treatment consisted of 25 g 'Glucodin' Glucose Powder (Boots Healthcare Australia Pty Ltd) dissolved in 300 ml water. The placebo treatment consisted of five 'Equal' tablets (10% Aspartame, The Merisant Company) dissolved

in 300 ml water. This quantity of aspartame was matched for sweetness with 25 g glucose powder when dissolved in 300 ml water (Sunram-Lea, Dewhurst, & Foster, 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 16 participants of the original 32 participants assigned to each test order. However, two thirds of the 25 participants included in the final data analysis were administered the glucose treatment in the first testing session, as six of the seven participants whom it was necessary to exclude from the final analysis were to be administered the glucose treatment in the second testing session

Materials

Modified California Verbal Learning Test-II (CVLT-II). The CVLT-II (Delis, Kramer, Kaplan, & Ober, 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, Sherman, & Spreen, 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 (of the 25 participants included in the analyses reported here, 13 were administered the standard form first, and 12 were administered the alternate form first). 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. Details pertaining to the timing of the modified CVLT-II recall phases are included in the Procedure section, below.

Simultaneously with encoding of the modified CVLT-II word lists, participants were required to perform a secondary motor task, to increase the difficulty of the memory task by dividing attention across the two tasks (Sünram-Lea et al., 2002). 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 Bond-Lader scale used here (Bond & Lader, 1974) has also been employed in other studies investigating nutrition, mood and cognitive functioning (e.g. Wesnes et al., 2003; Foster et al., 2007). This instrument requires participants to rate their level of ‘alertness’, ‘contentedness’, ‘calmness’ and ‘satiety’ on 19 bipolar scales. Three additional items were added to the original Bond-Lader scale for the purpose of the present study, in order to investigate self-reported fluctuations in satiety throughout the test session. 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’). The Bond-Lader scale used in this study is considered to be a useful measure of moment-to-moment fluctuations in mood and affect. A higher score indicates a higher level of the relevant dimension. This application of the Bond-Lader scale is consistent with previous work (e.g. Wesnes et al., 2003; Foster et al., 2007).

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 consistency and accuracy of MediSense Blood Glucose Meters has been reported to be very high (Matthews, Holman, Brown, Steenson, Watson, Hughes et al., 1987). According to the manufacturer’s user guide for the blood glucose test strips, the reliability of this

sampling procedure has been demonstrated, with the inter-assay variation for this sampling procedure ranging by no more than 2.9% to 5.1%. 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

Participants 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. Written informed consent was obtained prior to the first test session from participants and their parents. At this time, potential participants and their parents were informed that the the purpose of the study was to investigate the effect of glucose ingestion on memory performance. All test sessions began between 8:00 and 9:00 am. The first test session commenced with all participants being weighed. Height measurements were also obtained. Participants then 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, told only that they comprised of 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 (trials 1-5), followed by the modified CVLT-II interference word list. 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. Following the completion of the testing procedure, participants were offered a breakfast cereal meal, before returning to normal school classes.

A second testing session was conducted exactly one week subsequent to the first testing session. The second testing session was identical to the first testing session except that measurements of height and weight were not obtained. Participants were also administered the complementary treatment (glucose or aspartame) and version of the modified CVLT-II (standard form or alternate form) to that administered in the first testing session.

Results

Blood Glucose Concentration

A significant treatment x time interaction effect was observed, $F(3, 22) = 31.73, p < .001$, with a large effect size (partial $\eta^2 = .81$). Post-hoc pairwise t-tests revealed that, as anticipated, blood glucose concentrations were significantly higher for the glucose condition, relative to the placebo condition, 10 minutes, $t(24) = 6.81, p < .001$, 40 minutes, $t(24) = 8.35, p < .001$, and 60 minutes, $t(24) = 3.16, p < .01$, post-treatment delivery. Blood glucose concentrations between the glucose and placebo conditions did not differ at baseline, $t(24) = -0.90, n.s.$ Subsequent to glucose ingestion, post-hoc pairwise t-tests revealed that blood glucose concentrations within the glucose condition were significantly higher than baseline 10 minutes, $t(24) = -6.38, p < .001$, 40 minutes, $t(24) = -7.67, p < .001$ and 60 minutes, $t(24) = -3.17, p <$

.01, post-treatment delivery. Within the glucose condition, post-hoc pairwise t-tests also revealed that blood glucose concentrations were significantly higher 40 minutes post-treatment, relative to 10 minutes post-treatment, $t(24) = -3.24, p < .01$ and that blood glucose concentrations were significantly lower 60 minutes post-treatment, relative to 40 minutes post-treatment delivery, $t(24) = 5.85, p < .001$. As anticipated, post-hoc t-tests did not reveal any significant differences between blood glucose concentrations across the test session for the placebo condition (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.

A significant effect of time was observed on the alertness subscale, $F(3, 22) = 6.38, p > .01$, with a moderate effect size (partial $\eta^2 = .46$). Post-hoc Bonferroni pairwise comparisons revealed that self-rated alertness, collapsed across treatment conditions, was significantly higher 10 minutes post-treatment delivery than at baseline, $p = .001$. All other comparisons were nonsignificant on the alertness subscale.

A significant effect of time was also observed on the calmness subscale, $F(3, 22) = 7.83, p = .001$, with the effect size being large (partial $\eta^2 = .52$). Post-hoc Bonferroni pairwise comparisons revealed that self-rated calmness, collapsed across treatment conditions, was significantly lower 10 minutes post-treatment delivery than at baseline, $p = .001$. Overall self-rated calmness was also higher a) at 40 minutes

post-treatment, $p < .05$, and b) at 60 minutes post-treatment, $p < .05$, than c) at 10 minutes post-treatment.

There was also a significant effect of time on the satiety subscale, $F(3, 22) = 5.08$, $p < .01$, with a moderate effect size (partial $\eta^2 = .41$). Post-hoc Bonferroni pairwise comparisons revealed that self-rated satiety, collapsed across both treatment conditions, was significantly lower 60 minutes post-treatment than a) at 10 minutes post-treatment, $p = .01$, and b) 40 minutes post-treatment, $p < .01$.

No significant effect of time was observed on the contentedness subscale.

There was no significant effect of treatment on any of the four Bond-Lader subscales.

Modified CVLT-II

Immediate Free Recall. An analysis of free recall learning did not reveal any significant differences between the two treatment conditions across the five immediate free recall trials.

Short and Long Delay Recall. No significant effects of treatment were observed on any of the free or cued delayed recall phases of the modified CVLT-II. However, an analysis of the total items recalled at each recall phase in the two test sessions, collapsed across both treatment groups, demonstrated evidence of order effects between the two testing sessions. It is possible that any potential treatment effects were masked by this order effect. Therefore, treatment order was entered into the subsequent analyses as a between subjects factor, in order to enable systematic analysis of treatment x treatment order interactions.

Treatment x Treatment Order Interactions. A significant treatment x treatment order interaction effect was observed on short delay cued recall, $F(1, 23) = 19.93$, $p < .001$, long delay free recall, $F(1, 23) = 16.31$, $p = .001$, and long delay cued recall, $F(1, 23) = 10.55$, $p < .01$. Post-hoc pairwise t-tests revealed that on short delay cued

recall, long delay free recall and long delay cued recall, memory performance was significantly better in the glucose condition relative to the placebo condition for those participants who consumed the glucose treatment in the second testing session. For these three delayed recall phases, there was no significant difference between the glucose and placebo conditions for participants who consumed glucose in the first testing session (see Table 1). Significance values of all post-hoc tests reported here were Bonferroni adjusted.

INSERT TABLE 1 ABOUT HERE

Glucose regulation. The area under the glucose response curve (AUC) was calculated for each participant, as an indicator of that individual's glucoregulatory efficiency. A median split was subsequently performed on these data, to establish i) a group of better glucose regulators and ii) a group of poorer glucose regulators. Demographic and blood glucose data for each of these groups is displayed in Table 2. The poorer glucose regulators had a significantly elevated blood glucose concentration, relative to the better glucose regulators, 40 minutes and 60 minutes post-treatment delivery.

INSERT TABLE 2 ABOUT HERE

A significant treatment x treatment order interaction effect was observed for the better glucose regulators on short delay free recall, $F(1, 20) = 7.04, p < .05$, short delay cued recall, $F(1, 10) = 13.61, p < .01$, long delay free recall, $F(1, 10) = 13.47, p < .01$ and long delay cued recall, $F(1, 10) = 22.66, p = .001$. Specifically, post-hoc

pairwise t-tests (Bonferroni adjusted) revealed that on long delay free recall and on long delay cued recall, memory performance was significantly better in the glucose condition relative to the placebo condition for those participants who consumed the glucose treatment in the second test session (see Table 3).

INSERT TABLE 3 ABOUT HERE

Discussion

The present study investigated the effect of oral glucose administration and glucoregulatory efficiency on verbal episodic memory in healthy adolescents. Subsequent to the ingestion of a glucose laden drink or a sweetness matched placebo, participants were required to perform a secondary hand movement task during encoding of a supraspan word list. Blood glucose concentration was significantly elevated across the test session for the glucose condition, relative to the placebo condition.

It was hypothesised prior to the present study that ingestion of glucose would facilitate memory performance, relative to the placebo control condition. An order effect was observed in the present study, in that improved memory performance was observed in the second test session, relative to the first test session, irrespective of whether the glucose or placebo treatment was administered. When these order effects were controlled for statistically, a significant glucose memory facilitation effect was observed on short delay cued recall, long delay free recall and long delay cued recall. This finding is in line with previous research suggesting that glucose facilitates memory in healthy young adults under conditions of divided attention at encoding

(Foster et al., 1998; Sünram-Lea et al., 2001, 2002; Riby, McMurtrie, Smallwood, Ballantyne, Meikle, & Smith, 2006).

The second hypothesis in the present study was that the glucose memory facilitation effect would be more pronounced in the poorer gluco regulators. In contrast to this hypothesis, glucose was observed to enhance memory, in a treatment order-specific manner, on both components of long delay recall for adolescents exhibiting relatively better glucose regulation, while no significant effect of glucose on memory was observed for the poorer gluco regulators.

For participants administered glucose in the second testing session, significantly more items were recalled subsequent to glucose ingestion, compared to the placebo received in the first test session, on the following measures: short delay cued recall, long delay free recall and long delay cued recall. This difference reflects the combined influence of order and glucose administration on verbal episodic memory. By contrast, the difference in the total number of items recalled between the glucose and placebo conditions for those participants who consumed glucose in the first session was not found to be significant for any of the CVLT-II recall phases. Given that treatment order was controlled for statistically in the data analysis, there is no reason to suspect that the findings of the study were compromised by the fact that treatment order was not counterbalanced in the final study sample.

To our knowledge, the present study represents the first report that the glucose memory facilitation effect can be extended to healthy adolescent participants. Evidence for glucose enhancement of memory has previously been reported in young adults (Foster et al., 1998; Sünram-Lea et al., 2001, 2002; Riby et al., 2006), elderly participants (Manning, Hall, & Gold, 1990; Parsons & Gold, 1992; Craft et al., 1994; Kaplan et al., 2000; Riby et al., 2004) and even in young infants, who demonstrate

greater remembering of a vocal sound (measured via head movements toward the source of spoken words) subsequent to glucose ingestion (Horne, Barr, Valiante, Zelazo, & Young, 2006). However, whether uniform neurocognitive mechanisms are responsible for subserving the observed glucose facilitation effects across all of these age groups is unknown. For example, the hippocampus is thought to be involved in the mediation of the glucose memory enhancement effect (Winocur, 1995; Riby, 2004), yet temporal lobe brain structures are known to undergo significant neuroanatomical development during childhood and adolescence (Giedd et al., 1999). Further, adolescents demonstrate a greater susceptibility to abnormally high stress levels relative to other age groups (Byrne et al., 2007), which may be relevant given that the glucose memory facilitation effect may be modulated by the established interaction between glucose administration and stress-related circulating glucocorticoid levels (Fernández-Real, Ricart, & Casamitjana, 1997; Gibson, Checkley, Papadopoulos, Poon, Daley, & Wardle, 1999; Gonzalez-Bono, Rohleder, Hellhammer, Salvador, & Kirschbaum, 2002; Smith, 2002). This question should be addressed in future research investigations.

The within subjects design is the most sensitive and powerful study design in this area of research, as this methodology permits participants to serve as their own control (Riby, 2004). However, the present study highlights the importance of controlling for treatment order effects when employing a within subjects design, even when using two independent but matched forms of the same task, such as the versions of the modified CVLT-II used in this investigation. This is especially important in context of the relative sensitivity of the glucose memory facilitation effect (Foster et al., 1998). Learning strategies, such as semantic clustering, are more likely to be employed during performance of cognitive tasks such as the CVLT-II, in which

stimuli are drawn from shared semantic categories (which are used as recall cues). Although purely speculative, a further possibility is that participants are likely to feel less stressed in the second testing session, owing to greater familiarity with the testing procedure. If this is the case, it may well be that glucocorticoid (i.e. cortisol) levels were higher during the first testing session, relative to the second testing session. This is relevant given that acute elevation of glucocorticoids is known to be detrimental to episodic memory performance when the to-be-remembered material is unrelated to the source of the stressor (for a review see Wolf, 2003). While it was beyond the scope of the present study to investigate systematically whether stress and glucocorticoid levels modulated memory performance subsequent to glucose ingestion, this question may be an avenue for future research in this area.

A further finding of the present study was that an order-specific glucose memory facilitation effect was observed for adolescents exhibiting relatively better glucoregulatory efficiency, but not in the relatively poorer glucose regulators. Interestingly, this finding is inconsistent with previous research reporting a glucose enhancement effect only in healthy young adults exhibiting poor glucose regulation (Craft et al., 1994; Messier et al., 1999). Craft et al. (1994) observed that a) older males with better glucose regulation, and b) younger males with poorer glucose regulation, demonstrated superior memory performance subsequent to glucose ingestion. However, quantitative blood glucose profiles were, in fact, similar for these two groups, a) and b) above (Craft et al., 1994). An implication of this finding is that rather than glucoregulatory efficiency *per se* determining susceptibility for glucose facilitation of memory, it may actually be that a glucose memory enhancement effect is observed only when blood glucose concentration is located within an optimal range to induce memory facilitation. This suggestion also appears consistent with the

observation that individual differences in glucoregulatory efficiency shift the inverted-U shaped dose-response curve (relating blood glucose concentration to memory performance) for the glucose memory facilitation effect (Parsons & Gold, 1992). Notwithstanding this suggestion, the blood glucose concentration observed after glucose treatment in the better glucoregulators in the present study (at which memory enhancement was observed) was considerably lower than the blood glucose concentration at which memory facilitation has been observed previously in adults with poorer glucose regulation (Craft et al., 1994; Messier et al., 1999). It is, however, possible that a different dose-response relationship exists for children and adolescents, and adults. This issue should be addressed in future research.

The large variation in methodology between studies in this area makes it challenging to draw clear comparisons between studies. For example, different studies have used diverse criteria for defining glucoregulatory efficiency. In the present study, and in other investigations (Kaplan et al., 2000; Awad et al., 2002; Sunram-Lea et al., 2008), AUC was used as a marker of glucoregulatory efficiency. However, other studies have used a range of criteria, including i) peak blood glucose concentration (Hall et al., 1989; Manning et al., 1990), ii) the extent of recovery to baseline levels after a pre-determined interval (Craft et al., 1994; Messier et al., 1997; Messier et al., 1999; Knott, Messier, Mahoney, & Gagnon, 2001; Meikle et al., 2004), iii) the change in blood glucose concentration between defined time-points (Riby et al., 2004), iv) β -cell function and insulin resistance (Kaplan et al., 2000) and v) results of an oral glucose tolerance test (Donohoe & Benton, 2000; Messier et al., 2003). AUC was selected as the measure of glucoregulatory efficiency in the present study, as this is the only measure of the increase in blood glucose after glucose intake that incorporates a range of measurements over time (Messier et al., 2003).

It is important to note that in the present study (and in human studies of the glucose memory facilitation effect more generally) reported blood glucose concentrations reflect the blood plasma concentration of glucose. Glucose crosses the blood-brain barrier via a facilitated glucose transport mechanism. However, plasma glucose concentration does not necessarily reflect the concentration of glucose in the extracellular fluid of the brain regions which mediate memory (McNay & Gold, 2002). On this basis, an alternative potential explanation of the present study finding that glucose only improved memory in adolescents exhibiting relatively better glucoregulatory efficiency is that the “better glucoregulators” may, in fact, have a greater capacity for facilitated glucose transport across the blood-brain barrier. This proposition is purely speculative. However, it may well be that although the observed plasma glucose concentrations in the “better glucoregulators” were relatively lower across the test session, hippocampal extracellular fluid glucose concentration in these individuals was relatively higher than the “poorer glucoregulators”, resulting in enhanced memory performance in the “better glucoregulators”.

One further limitation of the present study is that due to the restricted sample size, no analysis comparing the effects of glucose and glucose regulation on memory performance between male and female participants was afforded. This could be a potentially relevant consideration, given that the interplay between glucoregulation and gender is thought to be relevant with regard to the glucose memory facilitation effect (Craft et al., 1994). Future research in this area should investigate further the relationship between age and gender on glucose regulation, and the influence of this relationship on the glucose memory facilitation effect. The participants in the present study all exhibited blood glucose concentrations within normal limits (e.g. Messier, 2005). Therefore, it may also be of interest in future work to investigate the effect of

glucose on memory in adolescents exhibiting glucoregulatory efficiency outside of the normal range. In this context, it is important to note that the glucose load delivered to participants in the present study was 25 g, whereas the glucose load of a standard oral glucose tolerance test is 75 g. The relatively smaller glucose dose administered in the current study may therefore not be sufficient to detect impairments in glucoregulatory efficiency.

In summary, the present study investigated the effect of glucose ingestion on verbal episodic performance in healthy adolescents. Encoding of memory materials was undertaken under dual task conditions. A significant order effect was observed, in that superior performance was seen in the second testing session, relative to the first testing session, irrespective of treatment condition. When this order effect was controlled for statistically, the glucose memory facilitation effect was observed. When glucoregulatory efficiency was also considered, only the relatively better glucose regulators demonstrated the glucose memory enhancement effect. The findings of this study suggest that the glucose memory facilitation effect, previously observed in adults, can be extended to adolescents. Further research is warranted to investigate in greater depth the relationship between age, glucoregulatory efficiency, glucose dose and gender effects on memory.

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Table 1

CVLT-II delayed recall results for the first and second testing session for the glucose and placebo condition, arranged by treatment order.

Mean values are displayed, with standard deviations in parentheses.

| Modified CVLT-II recall phase | Glucose First | | | Placebo First | | |
|-------------------------------|---------------|------------|-------------|---------------|------------|----------|
| | Glucose | Placebo | <i>p</i> | Glucose | Placebo | <i>p</i> |
| Short delay free recall | 11.1 (4.8) | 13.7 (4.6) | - | 12.6 (4.7) | 11.3 (2.9) | - |
| Short delay cued recall*** | 12.8 (2.7) | 14.5 (3.9) | <i>n.s.</i> | 14.9 (3.5) | 11.2 (3.0) | .01 |
| Long delay free recall*** | 12.6 (3.5) | 14.7 (4.3) | <i>n.s.</i> | 14.2 (4.1) | 10.5 (3.8) | < .05 |
| Long delay cued recall** | 13.9 (2.9) | 15.1 (3.8) | <i>n.s.</i> | 14.8 (3.6) | 11.4 (3.5) | < .05 |

Treatment x Treatment Order Interactions: ** $p < .01$. *** $p < .001$

Table 2

Demographic details and blood glucose data for the better and poorer glucose regulation groups.

| | Better regulators | Poorer regulators | <i>p</i> |
|--------------------------------|-------------------|-------------------|-------------|
| Age (years) | 15.7 (0.9) | 15.5 (1.0) | <i>n.s.</i> |
| BMI (kg/m ²) | 22.6 (3.0) | 21.7 (5.0) | <i>n.s.</i> |
| Fasting blood glucose (mmol/L) | 5.3 (0.5) | 5.0 (0.5) | <i>n.s.</i> |
| 10-min blood glucose (mmol/L) | 6.1 (0.7) | 6.0 (0.6) | <i>n.s.</i> |
| 40-min blood glucose (mmol/L) | 6.2 (0.6) | 7.8 (0.6) | < .001 |
| 60-min blood glucose (mmol/L) | 5.3 (0.7) | 6.7 (1.2) | .001 |
| AUC ^a | 34.6 (27.4) | 117.6 (28.6) | < .001 |

^aThe equation for the AUC calculation for the glucose testing session (Awad et al., 2002; Sunram-Lea et al., 2008) is as follows: $[(BGC_{10} - BGC_0)/2] \times (10 - 0) + [\{ (BGC_{10} - BGC_0) + (BGC_{40} - BGC_0) \} / 2] \times (40 - 10) + [\{ (BGC_{40} - BGC_0) + (BGC_{60} - BGC_0) \} / 2] \times (60 - 40)$.

Table 3

CVLT-II delayed recall results for the first and second testing session for the glucose and placebo condition, arranged by treatment order, for the better glucoregulators.

| Modified CVLT-II recall phase | Glucose First | | | Placebo First | | |
|-------------------------------|---------------|------------|-------------|---------------|------------|-------------|
| | Glucose | Placebo | <i>p</i> | Glucose | Placebo | <i>p</i> |
| Short delay free recall* | 7.7 (4.9) | 12.8 (5.0) | <i>n.s.</i> | 13.6 (4.9) | 10.6 (3.4) | <i>n.s.</i> |
| Short delay cued recall** | 10.7 (1.7) | 13.4 (4.7) | <i>n.s.</i> | 15.6 (4.3) | 11.0 (2.8) | <i>n.s.</i> |
| Long delay free recall** | 10.1 (3.2) | 13.4 (5.5) | <i>n.s.</i> | 14.8 (5.1) | 10.2 (2.8) | < .05 |
| Long delay cued recall*** | 11.4 (2.1) | 14.3 (4.7) | <i>n.s.</i> | 15.6 (4.3) | 10.0 (3.5) | < .01 |

Treatment x Treatment Order Interactions: **p* < .05. ***p* < .01. ****p* < .001

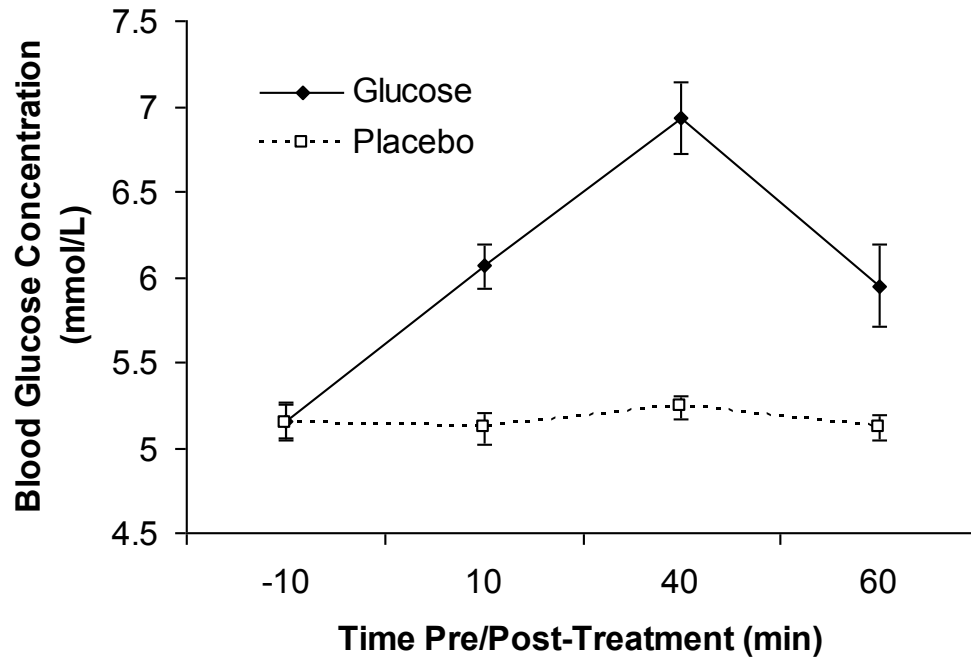


Figure 1

Blood glucose concentrations for the glucose and placebo treatment conditions.