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**Glucose enhancement of human memory:
A comprehensive research review of the glucose memory facilitation effect**

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Abstract

The brain relies upon glucose as its primary fuel. 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. This phenomenon has been termed the ‘glucose memory facilitation effect’. The purpose of this review is to discuss a number of salient studies which have investigated the influence of glucose ingestion on neurocognitive performance in individuals with a) compromised neurocognitive capacity, as well as b) normally functioning individuals (with a focus on research conducted with human participants). The proposed neurocognitive mechanisms purported to underlie the modulatory effect of glucose on neurocognitive performance will also be considered. Many theories have focussed upon the hippocampus, given that this brain region is heavily implicated in learning and memory. Further, it will be suggested that glucose is a possible mechanism underlying the phenomenon that enhanced memory performance is typically observed for emotionally laden stimuli.

Keywords: Glucose, memory, cognition

1. Introduction

The suggestion that glucose ingestion enhances cognition was first reported by Lapp (1981), in a study which found that healthy adolescents with higher blood glucose levels following a carbohydrate-rich meal displayed enhanced recall of word pairs relative to a fasting control group (Lapp, 1981; Messier, 2004). Subsequent early studies focused on glucose facilitation of memory in populations with cognitive deficits, such as the elderly, and patients with disorders involving memory impairment, including dementia, schizophrenia and Down's syndrome. It has been suggested that older individuals may benefit to a greater degree from glucose administration, as healthy young individuals are near to their 'cognitive peak' (Foster et al., 1998). However, there is now an abundant literature to suggest that under certain conditions, glucose can also enhance memory in healthy young adults. The present review will discuss the modulatory influence of glucose in a number of participant groups, including the 'healthy' elderly, individuals with cognitive impairment, and healthy young individuals. A number of potential neurocognitive mechanisms which may subserve the glucose memory facilitation effect will be put forward. It will then be suggested that endogenous glucose release into the bloodstream is the mechanism by which enhanced memory is observed for emotionally laden material.

2. General methods in glucose and memory research

Studies investigating the glucose memory facilitation effect typically involve the administration of a glucose treatment, which comprises powdered glucose (most often 25 g or 50 g) dissolved in water. A 'placebo' condition is also employed, in which participants are administered an artificial sweetener (aspartame or saccharin) drink, which optimally is sweetness and appearance matched with the glucose drink. Both between subjects and repeated measures designs are employed in this area of research, with participants either a) attending the laboratory once and being randomly assigned to the 'glucose' or the 'placebo' condition (between subjects), or b) attending the laboratory twice and completing both study conditions, in a counterbalanced order (repeated

measures). In order for treatment administration to take place when blood glucose concentration is at baseline, participants are usually required to fast for at least two hours prior to testing, with most studies requiring an overnight fast before a morning testing session. Cognitive testing then takes place during the ten minute to two hour post-ingestion time period, with blood glucose concentration peaking approximately 30 minutes post-ingestion before returning to baseline approximately two hours post ingestion (Donohoe and Benton, 2000). In order to reliably ascertain whether the glucose treatment has effectively modulated blood glucose concentration, blood glucose is typically measured via a finger prick pre-treatment, and at predetermined intervals post-treatment. Some researchers use these measures of blood glucose to determine an individual's glucoregulatory efficiency. It has been recently suggested by some authors that adjusting statistically for a variety of potentially confounding factors such as age (Craft et al., 1994; Riby et al., 2004), gender (Craft et al., 1994), body weight (Sünram-Lea et al., in press) and glucoregulatory efficiency (Craft et al., 1994; Smith and Foster, 2008), can influence the study outcomes.

3. Glucose, memory and 'healthy' ageing

Ageing is typically associated with some degree of forgetting and memory loss (Craik, 1994; Grady and Craik, 2000; Salthouse, 2003; Winocur, 1988). Much of the early human work investigating the influence of glucose ingestion on neurocognitive performance focused on elderly individuals. The rationale for theories which implicated glucose as a potential cognitive enhancer in elderly individuals was that ageing is accompanied by neuroendocrine dysregulation (Korol and Gold, 1998), including deficiencies in the regulation of key hormones involved in both memory storage and glucose regulation, such as adrenaline (Gold, 2005; Korol and Gold, 1998). In addition, poor glucose regulation is particularly prevalent in older individuals (Awad et al., 2002; Messier, 2004, 2005; Messier and Gagnon, 1996; Parsons and Gold, 1992).

Table 1 displays the findings of studies which have specifically investigated the influence of oral glucose ingestion in healthy elderly individuals (versus saccharin placebo) on various measures

of neurocognitive performance. Verbal episodic memory was the domain of cognitive functioning that was most frequently considered in these studies, with the majority of studies concluding that glucose improves verbal episodic memory performance in healthy elderly individuals (Hall et al., 1989; Manning et al., 1990; Manning et al., 1997; Manning et al., 1992; Manning et al., 1998; Parsons and Gold, 1992; Riby et al., 2006; Riby et al., 2004). Glucose was also observed to enhance performance in additional cognitive domains in this age group, including attention (Messier et al., 1997), design fluency, verbal fluency and visual memory (Allen et al., 1996).

One study in older individuals reported that glucose facilitation of verbal episodic memory occurred irrespective of whether glucose was administered a) pre-encoding or b) post-encoding of the to-be-remembered stimuli (Manning et al., 1992), while a further study by the same group found that glucose facilitated memory performance when glucose was administered a) pre-encoding or b) pre-retrieval of the to-be-remembered stimuli (Manning et al., 1998). On this basis, it can be inferred that an increase in blood glucose concentration via the administration of oral glucose enhances verbal episodic memory performance in older adults via a range of possible mechanisms (i.e. glucose modulation of memory is not specific to encoding, consolidation or retrieval). In both of these studies (Manning et al., 1992; Manning et al., 1998), glucose was observed to enhance verbal episodic memory when retrieval took place after a 24 hour delay.

One study in elderly individuals investigated the influence of carbohydrate delivery via potato and barley, with neither of these treatments yielding significantly improved neurocognitive performance relative to placebo (although glucose also failed to induce an enhancing effect on neurocognitive performance in this study; Kaplan et al., 2000). In addition, two further studies also investigated the role of glucose administration on verbal episodic memory under conditions of divided attention during encoding in older adults (involving performance of a secondary card sorting task; Riby et al., 2006; Riby et al., 2004). One of these studies reported that glucose was observed to improve memory performance irrespective of whether a secondary task was

implemented (Riby et al., 2004), while the other found that the glucose memory enhancement effect was not present under dual-task conditions (Riby et al., 2006).

In the study by Parsons and Gold (1992), participants presented for testing on four different days, separated by an interval of at least one week. In a counterbalanced order, participants received one of three glucose doses (10 g, 25 g, 50 g) or a saccharin placebo in each of the four test sessions. While glucose enhancement of verbal episodic memory was observed subsequent to ingestion of the 25 g glucose dose (relative to placebo), the 10 g and 50 g glucose doses did not induce a significant memory improvement when compared to placebo. It was therefore concluded that i) 25 g glucose is the optimal glucose dose to be administered in order to observe memory facilitation in elderly humans, and ii) the glucose memory facilitation effect follows an inverted-U shaped dose response curve in humans (Parsons and Gold, 1992). A meta-analytic review of the glucose memory facilitation effect subsequently replicated the finding that 25 g is the optimal glucose dose for inducing a memory enhancement effect subsequent to glucose ingestion (Riby, 2004). However, these findings (Parsons and Gold, 1992; Riby, 2004) are not consistent with other investigations of the glucose memory facilitation effect in older adults which have found that glucose improves verbal episodic memory performance subsequent to a 50 g glucose dose (Hall et al., 1989; Manning et al., 1990; Manning et al., 1997; Manning et al., 1992; Manning et al., 1998). On this basis, Parsons and Gold (1992) suggest that it may not be the size of the glucose dose *per se* that determines the effectiveness of glucose administration in facilitating memory performance. More specifically, the blood glucose concentration following the delivery of glucose appears to be the most relevant parameter (blood glucose concentration subsequent to a glucose load is modulated by various factors including, but not limited to, glucoregulatory efficiency and body mass index). Some animal studies have attempted to address the issue of body size as a potentially confounding factor, by administering a glucose dose that is dependent on body weight, and which therefore differs between participants (e.g. Messier, 1997; Salinas and Gold, 2005; Stone et al., 1992; Winocur, 1995; Winocur and Gagnon, 1998). However this procedure is not typically used in

human studies (c. f. Messier et al., 1998). Based on the results reported by Parsons and Gold (1992), it appears that the most effective blood glucose range for observing enhancement of verbal episodic memory in elderly individuals is approximately 8-10 mmol/L.

INSERT TABLE 1 ABOUT HERE

3.1 Glucoregulatory efficiency

As mentioned above, it is likely that glucose regulation modulates the glucose memory facilitation effect. This may especially be the case in older adults, who are more likely than younger individuals to experience glucoregulatory abnormalities (Dahle et al., 2009). In healthy individuals, blood glucose concentration typically peaks approximately 30 minutes following the ingestion of food, before decreasing to baseline levels within two hours. However, blood glucose typically remains higher for a longer period in individuals with poor glucose regulation (Donohoe and Benton, 2000). Poor glucoregulation is associated with memory impairment in both aged humans (Convit, 2005; Convit et al., 2003; Dahle et al., 2009; Kaplan et al., 2000; Lamport et al., 2009; Messier, 2005; Messier et al., 1997; Messier et al., 2003; Riby et al., 2004) and rodents (Greenwood and Winocur, 2001; Winocur, 1995). On a related note, brain glucose metabolism (including reduced and slowed capacity for facilitated glucose transport across the blood-brain barrier) is also known to become impaired as a consequence of ageing (Convit, 2005; Korol and Gold, 1998). This deficit may be mediated by the glucocorticoid stress hormone, cortisol (Convit, 2005). Impairments in glucoregulatory efficiency and brain glucose metabolism may be important when considering the role of glucose in modulating neurocognitive performance in the elderly.

A number of studies have specifically investigated the influence of glucoregulatory efficiency on the glucose memory facilitation effect in elderly humans. Craft and colleagues (1994) investigated the effects of age, gender and glucoregulation on cognitive performance. In this study, episodic memory improvements were observed in older adults exhibiting relatively better

glucoregulatory efficiency following glucose ingestion, but not in older adults exhibiting relatively poorer glucoregulatory efficiency. Conversely, memory enhancement following glucose ingestion was also observed in younger males exhibiting relatively poorer glucoregulatory efficiency, but not younger men exhibiting relatively better glucoregulatory efficiency. However, these findings (Craft et al., 1994) should be treated with caution. Overall, the older adults in this study had much poorer glucose recovery indices (used as a measure of glucoregulation) than the younger adults. Therefore, even those older adults exhibiting 'good' glucoregulatory efficiency in these studies may not be considered as 'normal' glucoregulators relative to the general population, given that their glucose recovery indices were comparable to the 'poor' glucoregulators in the young adult age group. Although speculative, it may well be the case that i) the blood glucose concentrations of the older adults with relatively better glucoregulatory efficiency and the younger adults with relatively poorer glucoregulatory efficiency in this study were within the optimal limit for inducing a facilitative effect on memory, rather than ii) glucoregulatory efficiency *per se* having a modulatory influence on the glucose memory facilitation effect. In addition to these findings by Craft and colleagues (1994), Messier and colleagues (1997) reported that in a study with elderly individuals, glucose enhanced the primacy effect on a paragraph recall task for better, but not poorer, glucoregulators.

More recently, research conducted by Kaplan and colleagues (2000) has demonstrated that poor glucoregulatory efficiency in healthy elderly individuals is associated with compromised cognitive ability, and that ingestion of glucose can reverse this deficit. Specifically, a regression analysis revealed that glucoregulatory efficiency predicts baseline episodic memory performance, with poorer glucoregulators exhibiting poorer baseline episodic memory ability (Kaplan et al., 2000). Further, glucose delivery to the bloodstream via a 50 g glucose drink, or via ingestion of barley or mashed potato was associated with episodic memory improvement relative to a placebo only for the relatively poorer glucoregulators in this study. Similarly, Messier and colleagues (2003) also reported that oral glucose ingestion attenuated the observed deficits in episodic memory

performance in those elderly participants who exhibited relatively poorer gluoregulatory efficiency.

Previous findings regarding the influence of gluoregulatory efficiency on the glucose memory facilitation effect in the elderly are therefore mixed. While glucose regulation appears to be an important modulatory variable, the results of some studies suggest that elderly individuals exhibiting relatively better gluoregulatory efficiency are more likely to demonstrate the glucose memory facilitation effect (e.g. Craft et al., 1994; Messier et al., 1997), while the findings of other previous work suggest that glucose enhancement of memory is more likely in poorer gluoregulators (e.g. Kaplan et al., 2000; Messier et al., 2003). This discrepancy between studies is difficult to explain, but may be related to the fact that most studies determine gluoregulatory efficiency groups by performing a median split on some measure of glucose response (such as recovery index). 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 defining gluoregulatory groups. This can bring about vast differences between studies in terms of whether the glucose concentration of the ‘good’ or ‘poor’ gluoregulators is within the optimal range to induce a cognitive benefit at the time of testing (according to the inverted-U dose-repose curve suggested by Parsons and Gold, 1992) and the arbitrary nature of median splits means that they are generally of no clinical relevance.

4. Glucose and memory in clinical populations with underlying memory deficits

Thus far, the present review has considered the effect of glucose administration on cognitive performance in healthy elderly individuals. The ingestion of oral glucose has also been robustly demonstrated to improve cognitive performance in a number of patients suffering from clinical syndromes associated with cognitive impairment. Disorders that have been considered in previous human studies investigating the role of glucose ingestion in modulating neurocognitive performance

include Alzheimer's disease, Down's syndrome, schizophrenia, mild head injury and mild cognitive impairment.

4.1 Alzheimer's disease

It is unsurprising that glucose has been investigated as a possible cognitive enhancer in patients suffering from Alzheimer's disease, given that this condition is associated with glucoregulatory abnormalities (Messier and Gagnon, 1996; Watson and Craft, 2004). Three key studies have specifically investigated whether glucose influences memory performance in patients with Alzheimer's disease. Firstly, it was reported by Manning and colleagues (Manning et al., 1993) that the ingestion of 75 g oral glucose attenuates deficits in episodic memory performance relative to a saccharin placebo in patients with Alzheimer's disease. Craft and colleagues (Craft et al., 1992) further reported that oral glucose ingestion enhanced verbal episodic memory performance in patients suffering from Alzheimer's disease exhibiting relatively poorer glucoregulatory efficiency, but not in healthy adults of a similar age who exhibited relatively better glucoregulatory efficiency. In a further study by the same group, cognitive performance was assessed in Alzheimer's patients under three conditions (fasting glucose, blood glucose concentration = 9.7 mmol/L and blood glucose concentration = 12.5 mmol/L), with a hyperglycaemic clamping procedure used to achieve target blood glucose concentrations (Craft et al., 1993). Verbal episodic memory performance was significantly enhanced following an increase in blood glucose to 12.5 mmol/L only, relative to performance following an overnight fast, for participants with very mild Alzheimer's dementia. At a subsequent follow-up 18 months following the original testing session, this same pattern of memory enhancement was observed for patients maintaining diagnostic criteria for very mild Alzheimer's disease. However, for those participants whose Alzheimer's dementia had progressed beyond the classification of 'very mild' over the 18-month interval between test phases, glucose facilitation of memory was no longer observed in either of the two glucose conditions (Craft et al., 1993).

From the findings of these three aforementioned studies (Craft et al., 1993; Craft et al., 1992; Manning et al., 1993), it can be inferred that glucose is effective as a cognitive enhancer in at least some patients with Alzheimer's disease. These findings also demonstrate the potential clinical significance of the glucose memory facilitation effect, in that glucose has been demonstrated to serve as an effective intervention against the key memory deficits experienced by Alzheimer's patients in these previous studies (Craft et al., 1993; Craft et al., 1992; Manning et al., 1993). However, it is important to note that only the study by Craft and colleagues (Craft et al., 1992) actually employed a group of healthy controls in order to directly compare the cognitive performance of Alzheimer's patients and healthy aged matched controls. It is therefore difficult to gauge from this series of studies whether glucose is more or less effective in terms of cognitive enhancement in patients with Alzheimer's disease or in healthy individuals. However, Manning and colleagues (Manning et al., 1993) mention that while attenuation of memory deficits was observed in Alzheimer's patients subsequent to glucose ingestion, the level of performance on the cognitive tests administered in the Alzheimer's patients did not reach the level that would be expected by a healthy individual. Future work in this area should a) focus on more detailed comparisons of memory performance subsequent to glucose ingestion in individuals with Alzheimer's disease and healthy controls, and b) further investigate the relationship between glucose ingestion, memory performance and glucoregulatory efficiency in Alzheimer's patients. It is of interest that Craft and colleagues observed a dissociation in terms of memory performance between individuals with Alzheimer's disease and healthy controls that was dependent on glucoregulatory efficiency. As mentioned previously in this review, the relationship between glucose ingestion, memory performance and glucoregulatory efficiency is likely to be complex. This may especially be the case in Alzheimer's disease, which is characterised by glucoregulatory abnormalities, potentially related to the apolipoprotein E (APOE) ϵ 4 allele. Alzheimer's patients who are non-carriers of this allele are known to be at risk of developing glucoregulatory complications (Messier, 2003; Watson and Craft, 2004). In addition, this relationship is further complicated by reports that increases in blood

insulin (in the absence of blood glucose increases) also enhance cognitive performance in individuals with Alzheimer's disease (Craft et al., 1996).

4.2 Schizophrenia

Episodic memory impairment is one of a number of prominent clinical features of schizophrenia (Stone and Seidman, 2008), and the role of glucose in attenuating cognitive impairment in this disorder has been investigated previously. Stone and colleagues (Stone et al., 2003) reported an improvement in verbal episodic memory performance in patients with schizophrenia subsequent to oral glucose ingestion. An additional study also observed an enhancement effect for verbal episodic memory subsequent to glucose ingestion (relative to placebo) in individuals with schizophrenia, but not in healthy or psychiatric (i.e. bipolar) controls (Newcomer et al., 1999). A further study by this same group also investigated the dose- and age-dependent nature of the relationship between glucose ingestion and cognitive performance in patients with schizophrenia (Fucetola et al., 1999). In this study, recognition memory performance was improved subsequent to ingestion of 50 g and 75 g glucose (relative to placebo) in older (> 42 years), but not younger (< 42 years), individuals with schizophrenia. However, enhancement of recognition memory performance was also observed subsequent to the 75g glucose dose in older healthy controls in this study. Spatial memory performance was also improved subsequent to ingestion of 50 g glucose in older patients with schizophrenia, and ingestion of 75 g glucose was observed to facilitate attention in younger patients with schizophrenia (Fucetola et al., 1999). On the combined weight of this evidence, glucose appears to be an effective cognitive enhancer in schizophrenia patients.

4.3 Mild head injury and mild cognitive impairment

The clinical significance of the glucose memory facilitation effect has been further demonstrated by two studies which have investigated the role of glucose in the enhancement of

memory in individuals with mild sports-related head injury (Pettersen and Skelton, 2000) and in older adults with mild cognitive impairment (Riby et al., 2009). In the study by Pettersen and Skelton (2000), healthy young adults who had sustained at least one concussion in the previous 10 years performed better on a test of verbal episodic memory subsequent to oral glucose ingestion, relative to placebo. Riby and colleagues (2009) also observed a glucose enhancement effect (relative to placebo) for elderly patients with mild cognitive impairment (defined as episodic memory impairment in the absence of executive dysfunction, impaired capacity for normal daily living, depression or delirium). However, a group of healthy elderly participants were also included in this study (Riby et al., 2009), with the healthy and mild cognitive impairment groups being indistinguishable in terms of the relative degree of glucose induced memory enhancement. In addition, the difference in verbal episodic memory performance between the glucose and placebo conditions in the study by Riby and colleagues (2009) did not reach statistical significance. On the basis of these two studies, there appears to be some support for the glucose memory facilitation effect in individuals with mild head injury or mild cognitive impairment, however more studies are needed to corroborate the findings of Pettersen and Skelton (2000) and Riby and colleagues (2009).

5. Glucose and memory in healthy young individuals

Over the course of the past 20 years, a number of studies have addressed the question of whether glucose can additionally influence neurocognitive performance in younger individuals, who are less likely to be suffering from cognitive difficulties than other participant groups (see Table 2). Similar to the body of research that has been conducted in elderly humans, much of this work has investigated glucose enhancement of verbal episodic memory, with a number of studies reporting that oral glucose ingestion enhances verbal episodic memory performance in healthy young adults (Benton et al., 1994; Foster et al., 1998; Meikle et al., 2004, 2005; Messier et al., 1998; Morris, 2008; Parker and Benton, 1995; Riby, McLaughlin et al., 2008; Riby et al., 2006;

Sünram-Lea et al., 2001, 2002a, 2002b, 2004). Notably, divided attention appears to play an important role in glucose facilitation of verbal episodic memory in younger individuals. Typically, studies in clinical populations do not employ a divided attention paradigm, which may explain why healthy control participants in such studies rarely exhibit a cognitive benefit from glucose.

5.1 Divided Attention

Some studies have incorporated a dual tasking paradigm, with participants performing a secondary task (e.g. performing sequences of hand movements) during encoding of a supraspan memory list (Foster et al., 1998; Riby et al., 2006; Sünram-Lea et al., 2001, 2002a, 2002b, 2004). Studies that incorporated a dual tasking procedure have all reported that glucose improves verbal episodic memory performance when memory materials are encoded under conditions of divided attention. However, a number of studies have failed to observe a glucose enhancement effect in healthy young adults for tests of verbal episodic memory in which memory materials were encoded under single task conditions (Azari, 1991; Benton and Owens, 1993; Hall et al., 1989; Manning et al., 1997; Scholey et al., 2001; Scholey and Kennedy, 2004; Winder and Borrill, 1998). In addition, further studies that have observed a glucose enhancement effect in the domain of verbal episodic memory under single task conditions in healthy young adults have reported an improvement only for primacy and/or recency items (Benton et al., 1994; Messier et al., 1998), or when a dichotic listening paradigm is employed (Parker and Benton, 1995). Morris (2008) observed a glucose enhancement effect in the domain of verbal episodic memory task under single task conditions. However, this was not a typical task of verbal episodic memory as the to-be-remembered information was incorporated within the narrative of a lengthy (~9 minutes) public safety video (Morris, 2008). Therefore, it is likely that this task was considerably more difficult than a typical verbal episodic memory task comprising recall of a supraspan word list. On the basis of the evidence discussed here, it can be concluded that glucose only *reliably* facilitates verbal episodic

memory in healthy young adults when memory materials are encoded under conditions of divided attention.

In a related study (Scholey et al., 2009a), a dual tasking paradigm was employed in which participants were required to perform an attention task which involved tracking a moving stimulus on a computer screen simultaneously with encoding of a supraspan word list, subsequent to ingestion of glucose or a saccharin placebo. Word list retention was tested by a recognition memory procedure, in which participants were required to distinguish studied words from foils (in the absence of the tracking task). Glucose ingestion was observed to improve tracking performance, but not recognition memory performance, in the healthy young adult participants. This study demonstrates that oral glucose ingestion can improve performance on non-memory tasks in healthy young adults, possibly by enhancing an individual's capacity to divide attention between two or more concurrent tasks (Scholey et al., 2009a).

5.2 Cognitive demand

A number of factors have been put forward in the literature which are suggested to alter the effectiveness of glucose as a cognitive enhancer. These include age, gender (Craft et al., 1994), glucoregulatory efficiency (Craft et al., 1994; Smith and Foster, 2008), trait anxiety (Smith et al., in press) and initial thirst (Scholey et al., 2009b). In addition, the glucose memory facilitation effect appears to be only reliably observed in healthy young adults when the cognitive demand of the task is high (e.g. Kennedy and Scholey, 2000; Meikle et al., 2004; Scholey et al., 2001; Sünram-Lea et al., 2002b). Foster and colleagues (1998) were the first to report that the ingestion of 25 g oral glucose enhances verbal episodic memory in healthy young adults under conditions of divided attention (namely, encoding of a supraspan word list concurrently with performing sequences of hand movements). A similar procedure has been associated with verbal episodic memory improvement in subsequent studies (Sünram-Lea et al., 2001, 2002a, 2002b, 2004). Specifically, in the study by Sünram-Lea and colleagues (2002b), glucose was observed to enhance verbal episodic

memory performance under dual-task conditions, but not under single-task conditions or when task difficulty was manipulated via increasing the length of the target list and by having participants remember the gender of the voice in which each of the target words were spoken. This study suggests that dual tasking, but not other types of cognitive demand, is required in order for glucose induced memory improvement to occur.

By contrast, a study conducted by Kennedy and Scholey (2000) provides evidence that glucose facilitation of memory in healthy young adults may be susceptible to task difficulty. The results of this study revealed that oral glucose ingestion did not enhance performance on serial threes (a test of attention and working memory in which participants are required to count backwards in threes) relative to placebo. However, performance on the more cognitively demanding serial sevens task (counting backwards in sevens) was enhanced following glucose ingestion, relative to placebo. A subsequent study employing a computerised serial sevens task replicated the finding that glucose facilitates serial sevens performance in healthy young adults (Scholey et al., 2001). Further, this study integrated a serial sevens control task in which participants were required to tap the number '5' four times on a numeric keypad, 20 times per minute (a task analogous to serial sevens, in that it requires comparable physical effort, but is much less cognitively demanding). It was reported that the reduction in blood glucose concentration associated with performance of the more cognitively demanding task (serial sevens) was greater than that associated with the less cognitively demanding control task. The findings of Scholey and colleagues (2001) provide further evidence that is consistent with the notion that glucose is more reliable in facilitating cognitive performance when the difficulty of the task is relatively higher. In addition, Meikle and colleagues (Meikle et al., 2004, 2005) have reported glucose enhancement of verbal memory only when the task demands are relatively more difficult (i.e. when to-be-remembered word lists are longer in length or when the individual items contain more letters). In one of the few 'divided attention' studies in this area which measured performance on both the primary and

secondary tasks, Scholey and colleagues (2009a) found that glucose actually improved tracking, but not verbal memory performance.

An interesting theory has emerged as a consequence of this body of research. It has been suggested that the performance of more cognitively demanding tasks is associated with greater depletion of circulating glucose, and therefore the provision of additional glucose is useful in 'topping-up' the supply of glucose to the brain (Scholey et al., 2006). This proposal has been predicated upon several studies in which the level of circulating glucose has been observed to fall more markedly after the performance of tasks involving relatively greater cognitive demand (Donohoe and Benton, 1999b; Fairclough and Houston, 2004; Scholey et al., 2001; Scholey et al., 2006), and is related to the concept that the brain utilises a considerable amount of energy for its relative size, while having a low capacity for glucose storage (Peters et al., 2004). The human brain is uniquely large among primates, and extensive evolutionary changes have been required in a relatively short period of time to ensure that the human body is able to provide adequate energy to fuel such a metabolically demanding organ (e.g. reduction in size of the human gastrointestinal tract and colon to support a high energy, but easily digestible diet; Saris et al., 2008). Related to the above, it has already been noted that an inverted-U dose-response curve underlies the glucose memory facilitation effect (Parsons and Gold, 1992; Riby, 2004). Although speculative, it may well be that during the performance of less cognitively demanding tasks, provision of even a small glucose dose may push the supply of glucose to the brain above the purported optimal level at which glucose enhancement of cognitive performance is typically observed. However, from an evolutionary perspective, it makes little sense that an individual should experience such a large and rapid reduction in circulating glucose as a consequence of performing a short (albeit demanding) cognitive task, as this could place an individual at risk of survival (due to relatively reduced glucose availability to the muscles if the individual was faced with a threatening situation). This reiterates the importance and ecological relevance of stress hormone mediated glucose release (as discussed further below). Alternatively, by contrast to the aforementioned hypothesis that glucose specifically

targets the hippocampus in modulating cognitive performance (Riby and Riby, 2006), the proposition that glucose only reliably enhances a) memory under conditions of divided attention in healthy young adults, as well as b) difficult tasks, may constitute evidence that glucose selectively enhances central executive functioning (Kennedy and Scholey, 2000).

5.3 Beyond verbal episodic memory

In accordance with the findings of Scholey and colleagues (2009a) discussed above, the findings of other previous studies have suggested that the ingestion of oral glucose can enhance domains of cognitive function beyond verbal episodic memory. Previous findings support a role for glucose in facilitating attention (Benton, 1990; Meikle et al., 2004; Reay et al., 2006), face recognition (Metzger, 2000), semantic memory (Riby et al., 2006), verbal fluency (Donohoe and Benton, 1999a), visuospatial functioning (Scholey and Fowles, 2002), visuospatial long-term memory (Sünram-Lea et al., 2001, 2002a, 2002b) and working memory (Hall et al., 1989; Kennedy and Scholey, 2000; Meikle et al., 2004; Reay et al., 2006; Scholey et al., 2001; Sünram-Lea et al., 2002b; 2004; see Table 2). Further, in addition to verbal episodic recall, oral glucose ingestion has been reported to enhance recognition memory for a supraspan word list in healthy young adults (Sünram-Lea et al., 2008; Sünram-Lea et al., 2001, 2002a, 2002b, 2004). Glucose has also been investigated as a possible cognitive enhancer when administered in combination with additional substances with known cognitively enhancing properties, such as caffeine (Scholey and Kennedy, 2004), ginkgo biloba (Scholey and Kennedy, 2004) and ginseng (Reay et al., 2006; Scholey and Kennedy, 2004). Specifically, glucose has been demonstrated to improve attention in healthy young adults when administered in combination with ginseng (Reay et al., 2006), and to improve attention and episodic memory when administered in combination with caffeine, ginseng and ginkgo biloba (Scholey and Kennedy, 2004).

INSERT TABLE 2 ABOUT HERE

5.4 The dose-response relationship

Messier and colleagues (1998) conducted a study to investigate the dose-response relationship between glucose ingestion and verbal episodic memory performance in healthy young women. A unique aspect of this study was that the glucose doses administered were based upon a specific quantity of glucose per kilogram of body weight. As mentioned previously, this procedure has been more typically employed in animal studies investigating glucose modulation of memory (e.g. Gold, 1986; Greenwood and Winocur, 2001; Messier, 1997; Messier et al., 1990; Salinas and Gold, 2005; Stone et al., 1992; Winocur, 1995; Winocur and Gagnon, 1998), whereas human studies typically involve the administration of a standard glucose dose that does not account for body weight. This may be a critically important factor in determining whether glucose ingestion modulates cognitive performance, as glucoregulatory efficiency differs between individuals of different body weights. In addition, the quantity of glucose delivery to the brain would be expected to differ between individuals of different body weights due to a number of factors including a) different rates of glucose utilisation as an energy substrate, and b) differences in circulating blood volumes. The only glucose dose that was reported to enhance verbal episodic memory performance in this study was the 300 mg/kg dosage, which was observed to enhance immediate recall of the first five items of a supraspan word list relative to placebo. Higher and lower glucose doses failed to confer any benefit in terms of immediate recall performance (Messier et al., 1998).

5.5 Methodological issues

In addition to the studies presented in Table 2, Owens and Benton (1994) investigated the role of oral glucose ingestion on inspection time and reaction time in healthy young adults. However, the authors of this study neglected to compare directly the influence of glucose ingestion on task performance. By contrast, performance was compared in individuals (from either the glucose or placebo treatment group) who exhibited an increase in blood glucose concentration by

the arbitrary value of greater than 1 mmol/L, relative to those who exhibited a decrease in blood glucose concentration of greater than 0.5 mmol/L (again, an arbitrary value). Faster reaction times were observed for the participants who exhibited increasing blood glucose concentration, relative to those participants who were found to exhibit a decrease in blood glucose concentration during the test session. The findings of this study (Owens and Benton, 1994) should be treated with caution, as it is difficult to determine on the basis of the results presented by the authors whether glucose ingestion *per se* has influenced reaction time, or whether some other factor(s) known to influence blood glucose concentration (such as stress hormone release) in fact contributed to the reported findings. Other aforementioned studies by this group have also used a similar, questionable data analysis strategy in concluding that glucose influences verbal episodic memory (Benton and Owens, 1993) and attention performance (Benton et al., 1994).

Interestingly, there are a number of differences with respect to the research methodology employed between the younger and older adult studies investigating the role of glucose as a cognitive enhancer. For example, all of the older adult studies presented in Table 1 utilised a within-subjects (repeated measures) design, whereas the younger adult studies have employed both within- and between-subjects designs. Arguably, repeated measures is a better study design, as each participant acts as their own control, thus eliminating any inter-individual differences. This may account somewhat for the relative lack of uniformity across the studies in young adults. Additionally, as discussed above, several of the studies conducted with young adult participants have employed a dual-tasking procedure, with the weight of evidence suggesting that glucose only reliably facilitates verbal episodic memory under conditions of divided attention. Only two older adult studies have incorporated a dual-tasking procedure (Riby et al., 2006; Riby et al., 2004). In contrast to the findings with younger adults, one of the aforementioned studies in the elderly actually reported that glucose failed to enhance verbal episodic memory performance when a secondary task was administered (Riby et al., 2006), with the other finding that glucose improved memory irrespective of whether a secondary task was administered (Riby et al., 2004). However,

one similarity between the older and younger adult studies relates to the finding that glucose is effective in facilitating verbal episodic memory performance irrespective of whether glucose is administered pre- or post-encoding (Manning et al., 1992; Sünram-Lea et al., 2002a).

An additional study which investigated the influence of oral glucose ingestion on memory performance in healthy middle-aged adults (40-63 years) was not included in either Table 1 or Table 2, as the participant group of this study cannot be classified as being either young or elderly individuals (Best et al., 2008). In this previous study glucose was not observed to influence verbal episodic memory or working memory performance relative to a treatment comprising a) a combination of saccharides or b) a placebo comprising natural sweetener (Best et al., 2008). The authors of this study suggest that the use of a natural sweetener placebo, as opposed to an artificial sweetener (e.g. aspartame, which would typically be used as a placebo in research investigations of memory modulation subsequent to oral glucose ingestion), may have contributed to this finding (Best et al., 2008). However, encoding of to-be-remembered materials in the verbal episodic memory task took place only under single task conditions. As mentioned above, studies in younger adults suggest that such task conditions may not be conducive to reliably observing a glucose memory enhancement effect.

6. Glucose modulation of memory in children

Very few studies have investigated the influence of oral glucose ingestion on acute neurocognitive performance in infants, children and adolescents. Children may be particularly sensitive to glucose enhancement of neurocognitive performance, given that the basal cerebral metabolic rate of children and adolescents is greater than that of adults (Chiron et al., 1992). This higher cerebral metabolic rate in children is related to the larger brain size of children, relative to body weight, in comparison to adults (Benton and Stevens, 2008). The first study to report the enhancing effect of glucose on verbal episodic memory performance was conducted with adolescent participants (Lapp, 1981; Messier, 2004). Subsequent to ingestion of a standardised oral glucose

tolerance test (OGTT) preparatory breakfast and 150 g glucose, improved performance was observed in this study in healthy adolescent participants for recall of low- and high-imagery paired associates, relative to a fasting control condition (Lapp, 1981). Recent findings from our laboratory have also observed an improvement in verbal episodic memory performance, under conditions of divided attention, in healthy adolescents, subsequent to glucose ingestion (Smith and Foster, 2008; Smith et al., in press; Smith et al., 2009). In one of these studies, further analyses suggested that glucose most reliably modulates memory in individuals with relatively higher trait anxiety (Smith et al., in press). In addition, two studies by Benton and colleagues have investigated the influence of glucose ingestion on neurocognitive performance in younger children. In one of these studies, children aged between 6 and 7 years demonstrated an enhanced capacity to sustain attention subsequent to a 25 g glucose load, relative to placebo, as measured by performance on a reaction time task (Benton et al., 1987). However, a subsequent study by the same authors failed to replicate these findings in children aged between 9 and 10 years (Benton and Stevens, 2008). Further, glucose failed to modulate spatial episodic memory performance in this age group (Benton and Stevens, 2008). On the other hand, oral glucose ingestion was associated with facilitation of verbal episodic memory, relative to placebo, in the 9-10 year old participants in this study (Benton and Stevens, 2008). Finally, it is worthwhile noting that oral glucose ingestion has also been associated with memory enhancement (less frequent turning of the head towards the source of spoken words as an index of habituation) in 2-4 day old infants (Horne et al., 2006). Therefore, on the weight of the aforementioned studies, it appears that glucose ingestion reliably modulates memory under conditions of divided attention in healthy adolescents, however more work is needed to ascertain the robustness of this effect across different domains of cognitive performance in younger children.

7. Neurocognitive mechanisms

Thus far, this review has suggested that the glucose memory facilitation effect has been reliably demonstrated in a) older adults, b) individuals with cognitive deficits, and c) healthy

younger individuals (under conditions of divided attention). However, the specific neurocognitive mechanisms which subserve this effect presently remain somewhat uncertain. While a number of theories relating to possible neurocognitive mechanisms have been put forward, robust evidence in support of either of these mechanisms has not yet been established in the literature. Each of these theories will be considered in this section. Much of the work investigating the specific neurocognitive mechanisms which mediate the glucose memory facilitation effect have employed animal models, due to the difficulties associated with making direct interventions in the human central nervous system. Firstly, a prominent theory pertaining to the anatomical brain region targeted by glucose in modulating cognitive performance (namely the hippocampus) will be presented. Secondly, a number of more specific mechanisms that have been proposed in the literature will be discussed.

7.1 The 'hippocampus hypothesis'

It is widely accepted that the hippocampus is a key structure mediating episodic memory functioning (Shastri, 2002). Related to this notion, the hippocampus has been implicated as being crucially involved in glucose enhancement of memory, given that episodic memory is the domain of cognition that has been most reliably demonstrated to benefit from glucose ingestion (Riby, 2004). This supposition has been termed the 'hippocampus hypothesis' (Riby and Riby, 2006).

In addition to those studies which have suggested that glucose ingestion most reliably improves episodic memory performance, other sources of evidence have also been put forward implicating the hippocampus in the glucose memory facilitation effect. Firstly, Winocur (1995) employed a conditional discrimination learning task with young and aged rats following injection of glucose or saline. The conditional discrimination learning task involves the conditioning of different responses to different stimuli; it is known to tap the resources of the prefrontal cortex. However, Winocur (1995) postulated that increasing the delay between stimulus offset and response in this task also requires involvement of hippocampally-mediated episodic memory. Following a 5 s or 15

s delay between stimulus onset and the time at which rats were able to make a response, enhanced memory for the stimulus was observed in the aged rats following glucose injection, relative to injection of saline. However, no memory facilitation was observed following glucose injection in the absence of a delay between stimulus offset and response. Given that the no delay condition is postulated to tap the resources of the prefrontal cortex, whereas the 5 s and 15 s delay conditions are also suggested to involve the hippocampus, this study suggests that glucose enhancement may be specific to memory processes which tap the resources of the hippocampus (Winocur, 1995).

Further evidence that the limbic region underpins the glucose memory facilitation effect is derived from a study which employed the ‘remember-know’ paradigm subsequent to ingestion of glucose or a placebo treatment (Sünram-Lea et al., 2008). This paradigm requires participants to identify whether they ‘remembered’ (i.e. recognition accompanied by recollection of contextual details; analogous to ‘recollection’), ‘knew’ (i.e. lack of contextual details retained; thought to reflect ‘familiarity’ processes) or ‘guessed’ whether recognised items had been part of the study list. Following glucose ingestion, participants were observed to correctly produce a significantly greater number of ‘remember’ responses to target items than participants who were administered a placebo treatment. By contrast, there were no between group treatment-related differences in ‘know’ or ‘guess’ responses. Given that ‘recollection’ based recognition memory, but not ‘familiarity’ is thought preferentially to involve the hippocampus (Aggleton and Brown, 2006), these findings (Sünram-Lea et al., 2008) further implicate the hippocampus as the brain region that is centrally involved in mediating the glucose memory enhancement effect.

Additional evidence for hippocampal mediation of the glucose memory facilitation effect can be drawn from a functional magnetic resonance imaging (fMRI) study conducted by Stone and colleagues in patients with schizophrenia (Stone et al., 2005). The primary finding of this study was that glucose ingestion was associated with significantly enhanced parahippocampus activation during verbal encoding, relative to placebo. These results imply that the medial temporal brain region is crucially involved in subserving the glucose memory facilitation effect. Further, event-

related potentials (ERPs) have also been employed to address the question of whether glucose specifically targets the hippocampus in modulating memory performance. In a previous study from our laboratory (Riby, Sünram-Lea et al., 2008), participants performed an oddball task subsequent to the ingestion of oral glucose or placebo, while ERPs were recorded. Glucose administration was associated with reduced P3b amplitude (known to reflect memory updating processes; Polich and Criado, 2006) relative to placebo. However, two ERP components that are associated with attentional processing (P2 and P3a) were not observed to be modulated by glucose. These findings were interpreted as demonstrating that glucose enhances memory by decreasing the cognitive resources required for memory updating (Riby, Sünram-Lea et al., 2008). P3b is known to be dependent on the hippocampus, whereas the P2 and P3a components are not, providing further evidence for the hippocampus hypothesis. By contrast, a further recent study from our laboratory (Smith et al., 2009) has suggested that glucose ingestion enhances ERP components of recollection (left parietal old/new effect) and familiarity (FN400) in adolescents. Given that recollection, but not familiarity, is thought to be supported by the hippocampus, this study suggests that glucose may target more global brain regions in modulating memory (Smith et al., 2009). In addition, this finding is further supported by previous studies in which a benefit of glucose ingestion was observed for tasks that are not directly subserved by the hippocampus (e.g. Kennedy and Scholey, 2000). Therefore, further work is clearly needed to elucidate the specific role of the hippocampus in mediating the glucose memory facilitation effect. Neuroimaging techniques, such as fMRI and fluorodeoxyglucose-positron emission tomography (FDG-PET) are likely to be useful in determining the specific regions of the brain that are most metabolically active subsequent to glucose ingestion, during cognitive task performance.

7.2 Specific mechanisms

In addition to those studies which have attempted to explain whether glucose specifically targets the hippocampus or more global brain regions in enhancing neurocognitive performance,

several studies have considered more specific mechanisms of glucose action on the central nervous system which could account for the observed findings pertaining to glucose modulation of memory. Glucose effects on i) cerebral insulin, ii) acetylcholine (ACh) synthesis, iii) potassium adenosine triphosphate (K_{ATP}) channel function and iv) brain extracellular glucose availability have all been postulated as potential mediators of the glucose memory enhancement effect. Each of these theories will now be considered.

7.2.1 Insulin. Insulin receptors are densely concentrated in the hippocampus relative to other brain regions (Unger et al., 1989). Given that verbal episodic memory is the domain of cognitive performance that has been most reliably demonstrated to be modulated by glucose ingestion, glucose-mediated insulin delivery to the hippocampus has been suggested as a candidate mechanism underlying the glucose memory facilitation effect (Craft et al., 1993; Craft et al., 1994). It has been proposed that insulin can directly influence memory functioning (Martins et al., 2006; Watson and Craft, 2004). Specifically, studies that have involved the intranasal infusion of insulin (i.e. direct delivery of insulin into the central nervous system) have suggested that insulin administration can enhance memory performance in the absence of changes in plasma glucose or insulin (Reger et al., 2006; Reger, Watson, Green, Baker et al., 2008; Reger, Watson, Green, Wilkinson et al., 2008). Craft and colleagues (1994) observed a gender difference in glucose facilitation of memory, in that glucose was observed to facilitate episodic memory in males, but this effect was not observed in female participants. This observation was attributed by these researchers to the higher rate of insulin induced glucose utilisation typically observed in males. However, although insulin appears to be an effective cognitive enhancer in its own right, it is difficult to ascertain reliably whether insulin effects on the hippocampus mediate the glucose memory facilitation effect. This is because it is not logistically practicable to conduct studies in humans in which plasma glucose concentration is increased in the absence of an endogenous rise in blood insulin levels. Therefore, the hypothesis that insulin mediates the relationship between glucose

ingestion and memory remains rather speculative; indeed, in some respects this may be considered a re-statement of the glucose memory facilitation effect, at least with respect to the endogenous state.

7.2.2 ACh synthesis. A further proposed mechanism of the glucose memory facilitation effect is that glucose administration increases the rate of hippocampal acetylcholine (ACh) synthesis. This line of research originated from evidence that glucose metabolism is involved in the synthesis of ACh (Messier, 2004). Early animal work reported that administration of glucose attenuated the amnesic effect of scopolamine injection (Durkin et al., 1992; Messier et al., 1990). Further, a sodium-dependent high-affinity choline uptake assay (Messier et al., 1990) and *in vivo* microdialysis (Durkin et al., 1992) suggested that this finding was mediated by increased ACh synthesis.

Ragozzino and colleagues (Ragozzino et al., 1996) employed an animal model to systematically investigate memory performance and hippocampal ACh output (measured via *in vivo* microdialysis) following administration of either a) saline, or a glucose dose of b) 100 mg/kg, c) 250 mg/kg or d) 1000 mg/kg. Rats displayed greater memory, assessed by performance on a maze task, following the 250 mg/kg glucose dose relative to those rats administered the saline control solution. The activity associated with performing the maze task increased hippocampal ACh synthesis relative to during rest. Moreover, ACh output was increased further following the 250 mg/kg glucose dose, relative to the saline control group, during performance of the maze task. These findings demonstrate that glucose (250 mg/kg) administered to rats is associated with a) increased hippocampal ACh output, and b) enhanced memory performance. Therefore, on the basis of these results, it appears that glucose administration may facilitate memory by directly increasing hippocampal ACh synthesis in a dose dependent manner. These results were subsequently extended, in that injecting glucose into the hippocampus unilaterally was observed to increase ACh output from both the ipsilateral and contralateral hippocampus (Ragozzino et al., 1998).

In order to further develop an understanding of the relationship between hippocampal ACh output, glucose and memory, Kopf and colleagues (Kopf et al., 2001) investigated the effect of

glucose and choline (which are precursor metabolites of ACh) on memory performance in a maze task. First, it was observed that 30 mg/kg glucose injected into the mouse hippocampus enhanced task performance, relative to injection of saline. Injection of 60 mg/kg choline chloride had a similar enhancing effect upon performance of the maze task, relative to saline controls. Furthermore, following the combined administration of 10 mg/kg glucose and 20 mg/kg choline chloride, memory enhancement was observed, even though these doses of glucose and choline chloride were not observed to enhance memory performance when administered independently of one another. 10 mg/kg glucose also does not typically raise blood glucose levels significantly above baseline. Therefore, Kopf and colleagues (2001) conclude that the observed memory enhancement resulted from increased hippocampal ACh synthesis, which was made possible by the availability of additional glucose - a biosynthetic precursor of ACh. The suggestion that ACh is a potential mediator of the glucose memory facilitation effect therefore appears feasible.

7.2.3 K_{ATP} channel function. Glucose has also been proposed to possibly influence memory via its effects on K_{ATP} channel regulation. The K_{ATP} channel is sensitive to glucose metabolism, in that glucose causes channel blockade by increasing intra-neuronal ATP levels. In this state, the neuron becomes depolarised, and therefore mediates neurotransmitter release (Stefani and Gold, 2001; Stefani et al., 1999). In order to test whether this mechanism may subservise the glucose memory facilitation effect, Stefani and colleagues (1999), investigated the influence of a) glucose, b) a K_{ATP} channel blocker or c) saline injected into the septum of rats on spatial working memory performance. Administration of either a) glucose or b) K_{ATP} channel blocker enhanced task performance relative to placebo, and lower doses of a) and b) administered in combination were also associated with improved task performance (although these smaller doses did not modulate task performance when administered in isolation). It was concluded that the similar task performance observed subsequent to both glucose and K_{ATP} channel blocker in this study can be taken as evidence that glucose may modulate cognitive functioning via its effects on K_{ATP} channel function (Stefani et al., 1999). This finding was replicated in a subsequent study by this same group

(Stefani and Gold, 2001). However, these conclusions should be treated with caution, as these studies do not directly investigate glucose effects on K_{ATP} channel function. The similarity in the observed findings for both the glucose and the K_{ATP} channel blocker conditions might imply that these two treatments are acting upon a common neurophysiological mechanism, or they may be exerting a similar outcome via different mechanisms. Studies that specifically quantify the K_{ATP} channel polarity subsequent to glucose ingestion and investigate subsequent neurocognitive performance may enable these questions to be addressed further.

7.2.4 Brain glucose availability. A further phenomenon has been observed that potentially provides a neurological explanation for the glucose memory facilitation effect, involving the measurement of brain extracellular glucose levels following cognitive testing in rodents. Traditionally, it has been suggested that glucose transporters maintain brain extracellular glucose levels at a constant rate (McNay and Gold, 1999, 2002). However, recent evidence has demonstrated that extracellular glucose levels differ between anatomical brain regions (McNay and Gold, 1999, 2002), and that hippocampal extracellular glucose levels fluctuate depending on the cognitive demand to which the limbic region is exposed (McNay et al., 2000; McNay and Gold, 2002). This phenomenon raises the possibility that glucose administration increases the localised availability of brain glucose during conditions of increased hippocampal demand, during which hippocampal glucose levels may otherwise become depleted. Note that this neurophysiological observation in rodents is in line with the previously described phenomenon that systemic plasma glucose levels are more rapidly depleted during tasks associated with relatively higher cognitive demand in humans (Donohoe and Benton, 1999b; Fairclough and Houston, 2004; Scholey et al., 2001; Scholey et al., 2006).

McNay and colleagues (2000) measured hippocampal extracellular glucose levels in rats prior to, during and subsequent to one of two spatial working memory tasks, differing in complexity, that are known to be reliant upon the hippocampus (and an additional control procedure, in which rats were placed in a box during the testing period). Thirty minutes prior to

behavioural testing, rats were administered a) 250 mg/kg glucose, b) saline or c) no treatment. For rats tested on the more difficult spatial working memory task that were administered either a) no treatment or b) saline, a fall in hippocampal glucose levels of 30% and 32% below baseline, respectively, was observed during the first five minutes of behavioural testing. These sub-baseline glucose concentrations were then observed throughout the remainder of the test session. By contrast, rats that completed the less difficult cognitive task did not exhibit this same degree of depletion in hippocampal glucose levels (i.e. the fall from baseline was 11% while performing this task for rats that were administered no treatment, and glucose levels returned to baseline in these rats before the end of the behavioural testing procedure). Further, on the more difficult spatial working memory task, rats that were administered glucose outperformed those rats that were administered saline or no treatment. By contrast, there was no difference in performance between the three treatment groups for those rats that completed the less difficult spatial working memory task. Together, these results suggest that glucose facilitates memory performance only on tasks that require greater cognitive demand. This is possibly due to the glucose treatment replenishing hippocampal extracellular glucose levels which were observed to become significantly more depleted during performance of the more cognitively demanding task.

In a subsequent study, McNay and Gold (2001) observed, as expected, that younger rats outperformed older rats on a spatial working memory task if no treatment was administered prior to cognitive testing. In accordance with this finding, the deficit in hippocampal extracellular glucose concentration was greater (and more prolonged) in aged rats relative to younger rats during task performance. However, no difference in cognitive performance was observed between young and aged rats when glucose was administered prior to task performance. Moreover, analogous to the earlier results reported by McNay and colleagues (2000), blood glucose concentration during testing was maintained at baseline levels for both groups when the task was performed subsequent to the delivery of glucose to the bloodstream (McNay and Gold, 2001). This finding accounts well for the finding that the degree of memory enhancement following glucose ingestion increases with age

(Meikle et al., 2004), and provides sound evidence for a neurobiological mechanism that may underlie this observation (replenishment of extracellular hippocampal glucose). Taken together, the results of these two studies (McNay et al., 2000; McNay and Gold, 2001) imply that a) greater enhancement of memory subsequent to a glucose load is observed as the task demands increase, and b) glucose is effective in facilitating memory performance by replenishing the supply of glucose to the hippocampus, which becomes diminished to a greater degree as the cognitive demand of the task increases.

8. The emotional memory effect

Emotionally laden material is typically better remembered than neutral stimuli (Hamann, 2001; LaBar and Cabeza, 2006). Exposure to an emotionally arousing stimulus leads to the rapid sympathetically mediated release of catecholamines (adrenaline and noradrenaline) from the adrenal medulla. In addition, a relatively slower stress-related neuroendocrine mechanism involves the hypothalamic-pituitary-adrenal (HPA) axis mediated release of glucocorticoids (cortisol in humans; Cahill and McGaugh, 1998; LaBar and Cabeza, 2006; McGaugh, 2004; van Stegeren, 2008; Wolf, 2008). Both catecholamines and glucocorticoids stimulate the endogenous liberation of glucose into the bloodstream, for the inferred purpose of providing the necessary energy to cope with a stressor (de Kloet et al., 2005). Adrenaline, noradrenaline and cortisol are assumed to play a role in subserving memory for emotionally laden material (Cahill and McGaugh, 1998; LaBar and Cabeza, 2006; McGaugh, 2004; van Stegeren, 2008; Wolf, 2008). However, adrenaline and noradrenaline do not readily cross the blood-brain barrier (Gold, 1995; Wenk, 1989), and must therefore exert an influence on memory via auxiliary mechanisms. It has been suggested that adrenaline and cortisol may influence memory for emotionally laden materials (at least in part) by increasing the supply of glucose to the brain (Brandt et al., 2006; Gold, 1995; Wenk, 1989). This ‘emotional memory effect’ may therefore be closely related to the glucose memory facilitation

effect (in that glucose may modulate cognitive performance, whether it is supplied exogenously or endogenously to the bloodstream).

In accordance with the aforementioned proposal that the emotional memory effect may be mediated by an increase in the supply of glucose to the brain, several studies have reported that exposure to emotionally arousing stimuli is associated with an increase in circulating blood glucose concentration. For example, Blake and colleagues (Blake et al., 2001) observed that exposure to emotionally arousing pictures is associated with an increase in circulating blood glucose concentration, relative to neutral pictures, and that memory for the emotionally arousing pictures was enhanced, relative to neutral pictures. In addition, Scholey and colleagues (2006) also reported that exposure to emotionally arousing stimuli (in this case, emotionally arousing words with a negative valence) led to an increase in blood glucose concentration. However, in this study, no memory enhancement effect was observed for the emotionally arousing items, relative to neutral items (Scholey et al., 2006). By contrast, memory enhancement for emotionally laden pictures in the absence of observable changes in blood glucose or salivary cortisol concentrations has been reported (Gore et al., 2006). Further, the question of whether oral glucose ingestion can confer an additional memory enhancement for emotionally laden to-be-remembered items has also been investigated. In one such study, better memory was observed for an emotionally arousing narrative, relative to a neutral narrative, and the emotional narrative was associated with an increase in blood glucose concentration (Parent et al., 1999). However, the ingestion of oral glucose was found to attenuate the emotional enhancement effect in this study (Parent et al., 1999). Similarly, Brandt and colleagues (2010; 2006) have reported that recognition memory performance is superior for negative emotionally laden words, relative to neutral and positive items, but oral glucose ingestion was not observed to modulate this effect. To summarise these findings, it appears that memory for emotionally arousing stimuli is relatively better than memory for neutral stimuli, a phenomenon which may be driven by increases in circulating glucose concentration. However, the provision of additional glucose does not further enhance this effect. According to the inverted-U dose response

relationship pertaining to glucose ingestion and memory performance, it may be that the provision of additional glucose to the brain, in addition to stress-hormone mediated increases in circulating glucose, pushes an individual's blood glucose concentration above the optimal range for observing a memory enhancement effect.

9. Summary and Conclusions

The modulation of cognitive performance subsequent to the ingestion of oral glucose is a phenomenon which has now been reliably demonstrated in a) older adults, b) younger adults (under conditions of divided attention) and c) individuals with clinical syndromes involving cognitive deficits. It is of course possible that a publication bias exists in this area of research, however on the weight of available published findings, this conclusion appears robust. Verbal episodic memory is the domain of cognition that appears to be most amenable to the glucose memory facilitation effect, possibly suggesting the involvement of the hippocampus in glucose enhancement of memory, although some other cognitive capacities have been relatively understudied. Individual differences in glucoregulatory efficiency may be important in determining whether an individual is more or less susceptible to experiencing a cognitive benefit subsequent to glucose ingestion. Further, in healthy young adults, glucose has only been reliably observed to enhance memory under conditions of increased cognitive demand, such as dual tasking. This may be related to the notion that healthy young adults are operating at their 'cognitive peak'; therefore, a cognitive enhancer would only be effective when such individuals face increased cognitive demands that allow 'room for improvement' (Foster et al., 1998).

A number of specific neurocognitive mechanisms thought to potentially underlie the glucose memory facilitation effect have been proposed. The most robust of these theories in terms of empirical evidence is the hypothesis that glucose enhances memory via its effects on ACh synthesis (Kopf et al., 2001; Ragozzino et al., 1998; Ragozzino et al., 1996). In addition, it has been reported that glucose administration replenishes the extracellular glucose levels of the rat hippocampus,

which become depleted during performance of demanding tasks (McNay and Gold, 2002). This phenomenon supports human studies which suggest that plasma glucose becomes depleted to a relatively greater degree during more demanding cognitive tasks (Donohoe and Benton, 1999b; Scholey et al., 2006). These studies imply that glucose enhances performance of more demanding cognitive tasks, as such tasks deplete the supply of glucose to the brain to a greater degree than relatively less demanding tasks.

It is also worthy of note that glucose-mediated modulation of memory may be the mechanism by which a memory advantage is observed for to-be-remembered emotionally laden material, relative to neutral stimuli. It has been noted above that hormones released in response to an emotionally arousing stimulus (cortisol, adrenaline and noradrenaline) stimulate glucose release into circulation. Therefore, it may well be that the memory enhancement that is typically observed for emotionally arousing material is mediated by glucose, implying that endogenous glucose release can also improve memory performance. For a conceptual model of the glucose memory facilitation effect as described in this review, see Figure 1.

INSERT FIGURE 1 ABOUT HERE

Research into the glucose modulation of memory has had both theoretical and practical applications. Theoretically, this area of research has enabled a better understanding of the cognitive neuroscience and neurochemical basis of memory. Practically, the importance of energy intake on cognitive performance is now better understood, particularly under conditions of divided attention, which has implications for dietary behaviours prior to cognitive activities demanded by school and work. Further, it is possible that manipulation of blood glucose could be beneficial in terms of future treatment for disorders involving cognitive impairment. For example, there is a well established association between type 2 diabetes and cognitive deficits, with improved glycaemic control via dietary intervention known to attenuate such deficits (Awad et al., 2004). It is possible

that treatments with glycaemic modulating properties, such as ginseng (Reay et al., 2006), could improve cognitive performance in patients with cognitive disorders. These two lines of research warrant further investigation in future studies.

In summary, the ingestion of oral glucose is known to enhance cognitive performance under specific conditions. Glucose has been most reliably associated with the modulation of verbal episodic memory. In healthy young adults and adolescents, encoding of memory materials under conditions of increased cognitive demand appears to be critical. Future neuroimaging studies (fMRI and FDG-PET) would be useful in reliably determining the specific brain regions involved in subserving the glucose memory facilitation effect.

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Figure Captions

Figure 1

A conceptual model of the glucose memory facilitation effect. The ingestion of oral glucose or acute stress/emotional arousal increases the concentration of circulating glucose in the periphery, and subsequently, the central nervous system. Via its proposed effects on a) insulin, b) ACh synthesis and/or c) K_{ATP} channel function, glucose enhances (verbal episodic) memory performance.

Table 1

Outcomes of studies investigating glucose modulation of memory in healthy elderly individuals. All studies below employed a repeated measures design and incorporated an overnight fasting regimen. Ticks indicate glucose enhancement of the specified cognitive domain, relative to a saccharin placebo. Dashes indicate that the specified cognitive domain was investigated, but no significant difference was observed between glucose and saccharin placebo conditions.

| Reference | Age (years) | Glucose Dose (g) | Attention | Design Fluency | Implicit Memory | Motor Function | Processing Speed | Semantic Memory | Verbal Episodic Memory | Verbal Fluency | Visual Memory | Working Memory |
|------------------------------------|-------------|------------------|-----------|----------------|-----------------|----------------|------------------|-----------------|------------------------|----------------|---------------|----------------|
| Hall et al. (1989) | 58-77 | 50 | | | | | | | ✓ | | — | — |
| Manning et al. (1990) | 62-84 | 50 | — | | | — | | | ✓ | | — | — |
| Manning et al. (1992) ^a | 60-81 | 50 | | | | | | | ✓ | | | |
| Parsons & Gold (1992) | 60-82 | 10 | | | | | | | — | | | |
| Parsons & Gold (1992) | 60-82 | 25 | | | | | | | ✓ | | | |
| Parsons & Gold (1992) | 60-82 | 50 | | | | | | | — | | | |
| Allen et al. (1996) | 61-87 | 50 | — | ✓ | | — | | | | ✓ | ✓ | |

| | | | | | | | |
|------------------------------------|--------------------|-----------------|---|---|---|----------------|---|
| Manning et al. (1997) | 61-80 | 50 | | — | | ✓ | |
| Messier et al. (1997) ^b | >55 | 50 | ✓ | | | — | — |
| Manning et al. (1998) ^c | 60-83 | 50 | | | | ✓ | |
| Kaplan et al. (2000) | 60-82 | 50 ^d | — | | | — | |
| Riby et al. (2004) | 60-80 | 25 | | | — | ✓ ^e | — |
| Riby et al. (2006) | $M = 68, SD = 5.9$ | 25 | | | — | ✓ ^f | — |

^aGlucose modulation of memory was observed in this study irrespective of whether glucose was administered pre-encoding or post-encoding. ^bThis study included ‘glucoregulatory efficiency’ as a further condition, which yielded numerous treatment x glucoregulatory efficiency interaction effects in addition to the main effects of treatment (demonstrating overall enhanced cognitive performance subsequent to glucose ingestion). ^cGlucose modulation of memory was observed in this study irrespective of whether glucose was administered pre-encoding or pre-retrieval. ^dTwo further conditions delivered 50g carbohydrate via a) mashed potato and b) barley, however neither of these conditions were associated with enhanced memory performance. ^eGlucose enhancement observed irrespective of whether a secondary task was administered. ^fGlucose enhancement not observed when a secondary task was administered.

Table 2

Outcomes of studies investigating glucose modulation of memory in younger adults. Ticks indicate glucose enhancement of the specified cognitive domain, relative to a saccharin or aspartame placebo. Dashes indicate that the specified cognitive domain was investigated, but no significant difference was observed between glucose and placebo conditions. The divided attention column indicates whether participants were required to encode memory materials under dual task conditions in studies in which verbal episodic memory was investigated. The design column indicates whether a between- or within- subjects design was employed for the glucose versus placebo comparison.

| Reference | Age (years) | Glucose Dose | Divided Attention | Design | Attention | Executive Functioning | Face Recognition | Recognition Memory | Semantic Memory | Verbal Episodic Memory | Verbal Fluency | Visuospatial Functioning | Visuospatial Memory | Working Memory |
|------------------------------------|----------------------|------------------------|-------------------|---------|-----------|-----------------------|------------------|--------------------|-----------------|------------------------|----------------|--------------------------|---------------------|----------------|
| Hall et al. (1989) | 18-23 | 50 g | No | Within | | | | | | — | | | — | ✓ |
| Benton (1990) | $M = 20.3, SD = 1.7$ | 25 g | N/A | Between | ✓ | | | | | | | | | |
| Azari (1991) | 19-25 | 30 g | No | Within | | | | — | | — | | | | |
| Azari (1991) | 19-25 | 100 g | No | Within | | | | — | | — | | | | |
| Benton & Owens (1993) ^a | $M = 21.6, SD = 4.8$ | 50 g | No | Between | | | | | | — | | | — | |
| Benton et al. (1994) | $M = 21.5$ | 50 + 25 g ^b | No | Between | — | — | | | | ✓ ^c | | | | |

| | | | | | | | | | | | |
|--|----------------------|---------------------|------------------|---------|----------------|---|---|---|---|---|---|
| Sünram-Lea et al. (2002a) ^h | 19-26 | 25 g | Yes | Between | | | ✓ | ✓ | | ✓ | — |
| Sünram-Lea et al. (2002b) | 18-29 | 25 g | Yes ⁱ | Between | | | ✓ | ✓ | | ✓ | ✓ |
| Meikle et al. (2004) | $M = 21.8, SD = 3.3$ | 25 g | No | Within | — | — | | ✓ | — | — | — |
| Meikle et al. (2004) | $M = 21.8, SD = 3.3$ | 50 g | No | Within | — | — | | ✓ | — | — | — |
| Meikle et al. (2004) | $M = 38.4, SD = 6.7$ | 25 g | No | Within | ✓ | — | | ✓ | — | — | ✓ |
| Meikle et al. (2004) | $M = 38.4, SD = 6.7$ | 50 g | No | Within | ✓ | — | | ✓ | — | — | ✓ |
| Scholey & Kennedy (2004) | 18-32 | 37.5 g ^j | No | Within | — | — | | — | — | — | — |
| Sünram-Lea et al. (2004) | 18-28 | 25 g ^k | Yes | Between | | | ✓ | ✓ | | — | ✓ |
| Meikle et al. (2005) | 17-48 | 25 g | No | Between | | | | ✓ | | | |
| Reay et al. (2006) | $M = 21.9, SD = 4.6$ | 25 g | N/A | Within | ✓ ^l | | | | | | ✓ |
| Riby et al. (2006) | $M = 30.1, SD = 4.6$ | 25 g | Yes | Within | | | ✓ | ✓ | — | | |
| Morris et al. (2008) | 19-38 | 50 g | No | Between | | | | ✓ | | | |
| Riby et al. (2008) | 35-55 | 25 g | No | Within | | — | | — | | | — |
| Riby et al. (2008) | 35-55 | 50 g | No | Within | | — | | ✓ | | | — |
| Sünram-Lea et al. (2008) | 18-25 | 25 g | N/A | Between | | | ✓ | | | | |
| Scholey et al. (2009a) ^m | $M = 21.6, SD = 4.9$ | 25 g | Yes | Between | ✓ | | — | | | | |

^aThe specific treatment ingested (glucose or placebo) did not influence performance, but verbal episodic memory performance was significantly correlated with blood glucose concentration post-treatment ingestion. ^bA 25 g glucose top-up was administered 30 minutes subsequent to ingestion of the original treatment. ^cGlucose enhanced the primacy and recency effect (combined) only. ^dGlucose enhanced verbal episodic memory only for items dichotically presented to the right ear (i.e. left cerebral hemisphere). ^eGlucose enhanced the primacy effect only. ^fAlthough executive functioning performance was not found to be improved by glucose as measured by the Water Jars, Logical Reasoning, Block Design and Porteus Maze tasks, response times were faster on the Porteus Maze task in the glucose condition. ^gThe glucose effects were observed regardless of whether glucose was administered subsequent to a) overnight fast, b) 2-hour fast following standardised breakfast, c) 2-hour fast following standardised lunch. ^hMemory was enhanced regardless of whether glucose was administered before or after encoding. ⁱThree divided attention conditions were included: hand movements, key tapping, no divided attention. ^jThis quantity of glucose was effective in facilitating memory and attention when combined with 75 mg caffeine, 12.5 mg ginseng and 2 mg ginkgo biloba. ^kGlucose was administered in conjunction with a) full-fat yoghurt or b) fat-free yoghurt in this study, with glucose effects only being detected in the fat-free condition. ^lGlucose enhanced attention when administered alone or in combination with 200 mg ginseng. ^mIn this study, an attention (visual-motor tracking) task was used as a secondary task during word encoding; however, glucose enhanced performance of this task but not the primary recognition memory task.