THE IMPACT OF GLUCOSE AND GLUCOREGULATION ON MEMORY

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ABSTRACT

The effect of glucose on memory has been investigated for in excess of 25 years, with some consensus generated amongst the literature indicating that glucose has a facilitating effect. However, the robustness of the glucose effect has been questioned, with a considerable body of evidence reporting no glucose facilitation of memory. It has been suggested that glucoregulatory control may be a key mediating factor of the glucose effect. Glucoregulatory control and cognitive functioning are intrinsically linked, with cognitive impairments a common feature in populations presenting with poor glucoregulatory control such as diabetics, Alzheimer's disease sufferers, schizophrenics and the elderly. Although again the evidence has proven contradictory, with evidence to suggest that both better and poorer glucoregulators are more / less susceptible to the glucose effects on cognition.

Verbal declarative memory has been reported to be the most reliably enhanced aspect of memory to benefit from a glucose effect. However, it is not yet clear whether verbal declarative memory as a whole is being facilitated, or whether the different phases of memory (encoding, consolidation, retrieval etc.) are differentially targeted. Consequently the primary aim of this thesis was to evaluate the effect of glucoregulatory control and glucose, on the different phases of verbal declarative memory. This was achieved through the use of novel paradigms employed previously within the cognitive sciences literature.

Chapter 2 addressed a secondary aim of this thesis; investigating the current gap in the literature pertaining to the effect of glucose administration on cognition in children. Chapter 3 investigated the types of recognition (recollection and familiarity) that were made subsequent to a glucose load, using the 'remember/know' paradigm. Chapter 4 investigated encoding efficiency during the item method directed forgetting paradigm, in which participants actively attempt to forget specific stimuli through cessation of encoding. In chapters 5 and 6 the potential mediation of inhibition processes was explored, with both semantically related (Retrieval Induced Forgetting paradigm) and orthographically similar but semantically unrelated stimuli (Memory Blocking Effect paradigm).

The tentative evidence presented in this thesis indicates that glucoregulatory control may mediate the glucose facilitation effect during the encoding phase, with better regulators seemingly benefiting from greater encoding benefits than poorer following glucose. Glucose was not observed to influence inhibition processes, or types of recognitions made. However, better glucoregulators exhibited more efficient adaptive inhibition (overcoming inhibition of blocking items to continue searching the lexicon and increased inhibition of semantically related competing stimuli). Administration of glucose did not mediate cognition in children, with the exception of an impairment of performance on a challenging reaction time task following 20 g of glucose.

Memory phases are seemingly differentially affected by glucose administration, with the effect mediated by glucoregulatory control. Utilising the paradigms employed here (or similar) to investigate a range of populations presenting with cognitive decline / glucoregulatory control, would further allow the glucose and glucoregulatory effects on the different phases of memory to be further disentangled.

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AUTHOR'S DECLARATION

This work has not been submitted for any other award. In all experimental chapters of this thesis the author had sole responsibility for the data collection, analysis, and interpretation. The writing of this thesis is the sole work of the author.

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Signature:

Date: 13th August 2010

CHAPTER 1. INTRODUCTION.

1.1 General Introduction

Glucose is the primary energy source for the brain, which is the most metabolically expensive organ in the body. Despite this, paradoxically low levels of glucose (a key metabolic resource) are stored within the brain itself. Consequently brain functioning is coupled to the provision of circulatory glucose crossing the blood-brain barrier. Cerebral stores of glucose are only able to sustain functioning for approximately 10 minutes without supplementation from blood glucose (Marks and Rose, 1981). The limited amount of glucose stored as glycogen in the brain is primarily stored in the glial cells, the metabolism of which sustains glial cells as opposed to neurons (Swanson, 1992). Lactate produced during glucose metabolism can be transported from the glial cells into neurons for further metabolism (Pellerin and Magistretti, 1994). The importance of maintaining adequate glucose provision to the brain through tightly regulating circulatory blood glucose is highlighted in cases of hypoglycaemia, whereby cognitive impairments are quickly induced (these are considered later in this chapter), with prolonged deprivation leading to damage and even death. Whilst other resources may be utilised in the absence of glucose and glycogen stores (in the liver and muscles), for example Ketone bodies (also mannose, lactate and fatty acids but these make a very minor contribution), such resources are only utilised in extreme cases e.g. starvation.

Glucose utilisation in the brain is not constant across the lifespan. Blood flow and glucose utilisation in a resting state (Basal Metabolic Rate [BMR] in normal children is approximately twice that found in adults, the blood flow in a child's brain is approximately 102 ml/min/100 g as opposed to 57 ml/min/100 g in adults, with children's brain glucose utilisation rate of 10.8 mg /min/100 g as opposed to 5.5 mg/min/100 g in adults) (Kennedy and Sokoloff, 1957). The reason for this is twofold, firstly in children the brain accounts for a disproportionately large percentage of body mass and, secondly, extensive synthesis of new tissue is required in children, which is metabolically expensive. As this suggests, only a proportion of the glucose demanded by the brain is metabolised to provide energy (approximately 30%) (Chugani, 1998). Glucose is essential to the synthesis of amino acids, peptides, lipids and nucleic acids and notably in the synthesis of neurotransmitters such as acetylcholine (Benton, 2005).

Accordingly, the provision of glucose to the brain has afforded a considerable body of research assessing various aspects of cognitive function. For over 25 years, the

facilitating effect of glucose on memory has been studied. Research supporting the facilitative effect of raising circulatory glucose levels on modulating memory has generated some consensus amongst the literature. Consequently the facilitation effect of glucose on memory has been well accepted (for reviews see; Benton, 2001, Gold, 1991, Lieberman, 2003, Messier, 2004, Riby, 2004, White, 1991). However, the consistency of the glucose effect has been questioned elsewhere (e.g. Hoyland et al., 2008), with studies that report a lack of treatment effects of glucose in comparison to placebo not uncommon. While the research to date has made headway in identifying the areas of cognition and memory that are susceptible to glucose provision, there remains considerable scope to investigate a number of aspects which have not been considered. In particular the specific mechanisms by which glucose may be acting upon cognition remain to be fully understood, with several mechanisms presented as potentially modulating the glucose effect (see section1.4 for details of potential mechanisms).

Before considering the effects of glucose on cognition (memory in particular), it is first important to understand how glucose is processed and metabolised within the body, so that it can ultimately be utilised by the central nervous system (CNS), this is discussed below.

1.2 Digestion and Glucose Metabolism

1.2.1 The Digestive Tract

Glucose is obtained from the digestion of food in the gut (absorptive phase of metabolism), or from breaking down glycogen stores where insufficient exogenous glucose is available (fasting phase). The body reserves relatively little carbohydrate stores, with the quantity that is stored providing less than one days energy requirements, with fat in adipose tissue providing a longer term energy reserve (Hurlbert, 2007).

Following ingestion, food entering the digestive tract is broken down into carbohydrates, proteins and fats. Digestion begins immediately in the mouth, where salivary amylase enzyme begins to breakdown complex carbohydrates into simple sugars. Following transportation through the pharynx and oesophagus into the stomach, digestion of protein and fats begins. The stomach contains acid dependent proteinase enzymes which are responsible for initiating the protein digestion. This acidic environment also serves to kill bacteria whilst breaking down food. The partially digested food is stored in the stomach

for controlled slow release into the small intestine, retaining large particles for reduction prior to release. Once in the small intestine the chyme (partially digested food), is broken down via pancreatic enzymes (e.g. proteinase, lipase and amylase). The majority of the digestion products are absorbed (the passage of substances across from the gut into the interstitial fluid) by the small intestine, with the remainder passing to the colon. While little digestion occurs here, bacterial flora acting on dietary fibre form gases along with the synthesis of short-chained fatty acids and vitamins, which may then be absorbed (Dimaline, 2007).

1.2.2 Peripheral Glucose Metabolism

Glucose absorbed from digestion, or through the breakdown of glycogen, is transported through blood vessels around the body to be utilised as energy, released during oxidative metabolism. Glucose is also utilised in glycolytic cells which do not contain mitochondria, such as red blood cells, to form energy substrates and also by the brain which is almost entirely reliant on constant circulatory provision. Subsequently glucose homeostasis is tightly controlled to ensure constant levels of extracellular plasma supplies of glucose. The circulatory levels of glucose are primarily mediated through the actions of insulin and glucagon, produced in the pancreas (see sections 1.2.2 through to 1.2.4 on glucoregulation for more detail).

Carbohydrates may be broken down entirely to glucose, with other macronutrients providing smaller quantities (protein can be broken down to derive approximately 58% of its mass into glucose, and approximately 10% may be derived from fat / lipids), which occurs primarily in the liver and kidneys. The metabolism of glucose is the most efficient of the macronutrients (glucose metabolism produces 40% usable energy as opposed to 25-35 % usable energy from proteins, waste products e.g. heat comprise the remainder) (Hurlbert, 2007). Subsequently energy may be derived from the metabolism of proteins and fats. However, as some cells e.g. neurons and red blood cells, utilise glucose as their primary source of energy, the body retains tight glucoregulatory control of circulatory glucose levels to meet this demand. Availability of circulatory glucose is crucial to produce adenosine triphosphate (ATP), which is essentially the primary energy required for cellular processes. Disruption to the regulation of circulatory glucose levels, leads to serious cognitive and physical deficits. Defective glucoregulatory control is also a risk factor for several disorders.

Metabolism can be divided into catabolism and anabolism. The catabolic metabolic pathway by which glucose is broken down into pyruvate is glycolysis, which occurs in the cytosol. It is through this process that macromolecules are broken down into simple smaller molecules with the associated release of energy as ATP. Glycogen is broken down to produce glucose-1-phosphate during glycogenolysis, which can then enter the glycolytic pathway. Glycolysis delivers chemical energy as ATP, reduced nicotinamide adenine dinucleotide (NADH), reduced nicotinamide adenine dinucleotide phosphate (NADPH) and reduced flavin adenine dinucleotide ($FADH_2$). These energy carriers are used during the anabolic metabolism. Anabolic metabolism describes the synthesis of complex molecules from simpler ones, which requires net energy input. Glycogenesis refers to the synthesis of glycogen from glucose, with gluconeogenesis referring to glucose synthesis from non-carbohydrates e.g. lactate and some amino acids, primarily in the liver and kidneys. As the energy is given up from the carriers during anabolic metabolism, they are converted to adenosine diphoshate (ADP), NAD^+, $NADP^+$ and FAD. These are then regenerated through catabolism (Hurlbert, 2007).

Figure 1.1 shows the reactions involved during glycolysis. Firstly glucose is phosphorylated into glucose-6-phosphate, by the hexokinase enzyme utilising ATP. The majority of glucose-6-phosphate is converted to pyruvate; however, it can be diverted into the pentose-P shunt pathway at this point to generate NADPH (and five-carbon compounds) or converted into glucose-1-phosphate. Glucose-1-phosphate can be utilised to form glycogen (storing glucose) along with other compounds (galactose, glycoproteins and glycolipids) (Hertz and Dienel, 2002). The regulation of the glycolytic pathway is regulated by the activity of hexokinase under normal conditions (Lund-Andersen, 1979). Hexokinase activity regulates the rate of glycolysis and is mediated through; increased inorganic phosphate (Pi) concentration, increased ADP/ATP ratio (which both drive increased activity), and by increased glucose-6-phosphate (which decreases activity). The activity of phosphofructokinase and pyruvate kinase also regulates the rate of glycolysis. Both are increased by higher concentrations of ADP and inhibited by higher concentrations of ATP. In times of high energy utilisation, ATP is required, increasing the ratio of ADP/ATP and subsequently increasing the rate the glycolysis.

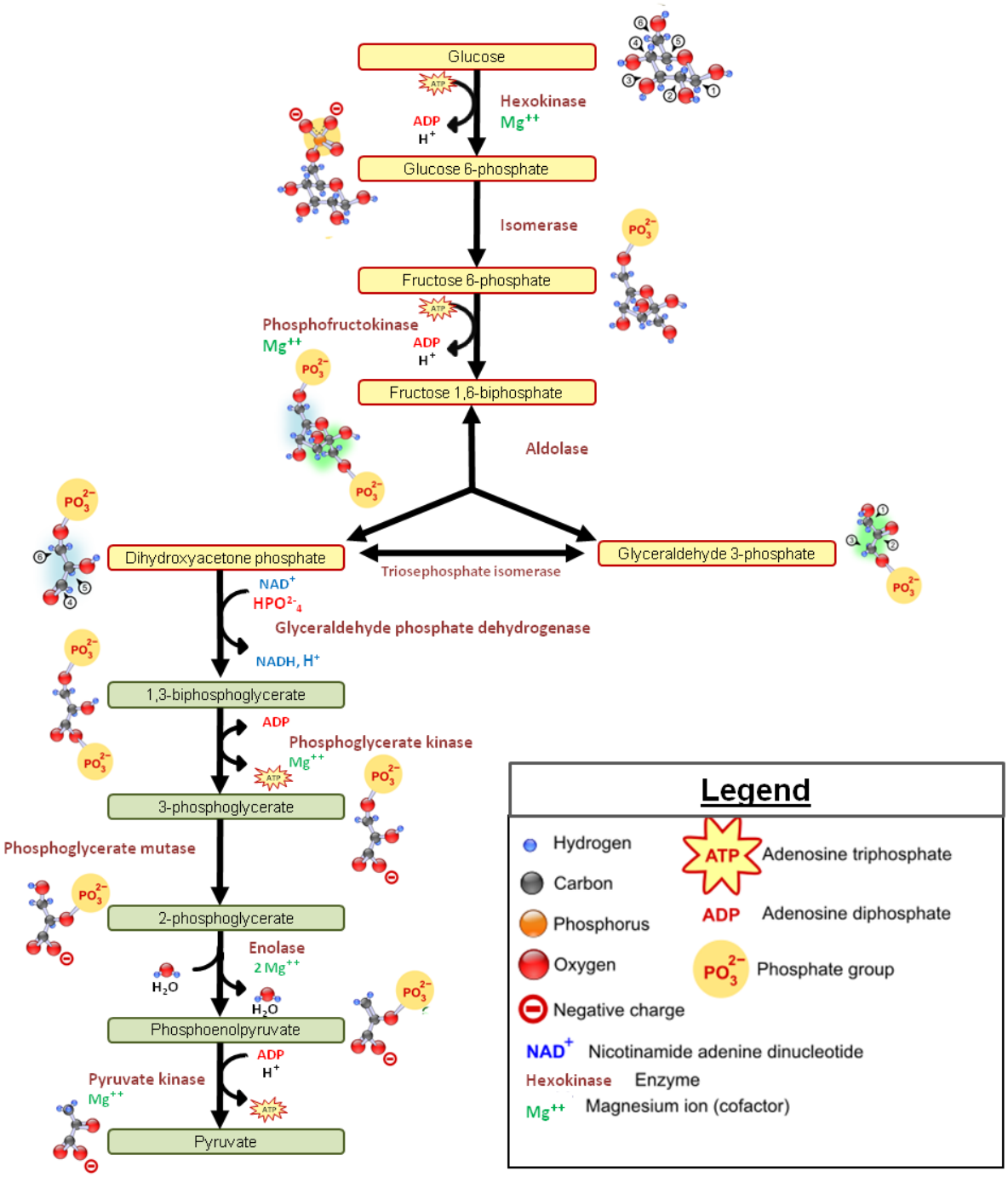

Figure 1.1 A schematic of the processes of glycolysis, from glucose to pyruvate *(Adapted from Mrabet, 2009)*.

Once glucose has been metabolised to pyruvate, it is actively transported into the mitochondria. Here the pyruvate is decarboxylated, combining with coenzyme A to produce acetylcoenzyme A (Acetyl-CoA) before entering the tricarboxylic acid (TCA) cycle (see figure 1.2 below). Glucose metabolism is completed in the TCA cycle with Acetyl-CoA converted to CO_2, NADH and $FADH_2$ through the actions of several enzymes. It is the production of NADH and $FADH_2$ which is the vital purpose of the TCA cycle. Production of NADH and $FADH_2$ releases electrons, which then feed the electron transfer to produce ATP energy.

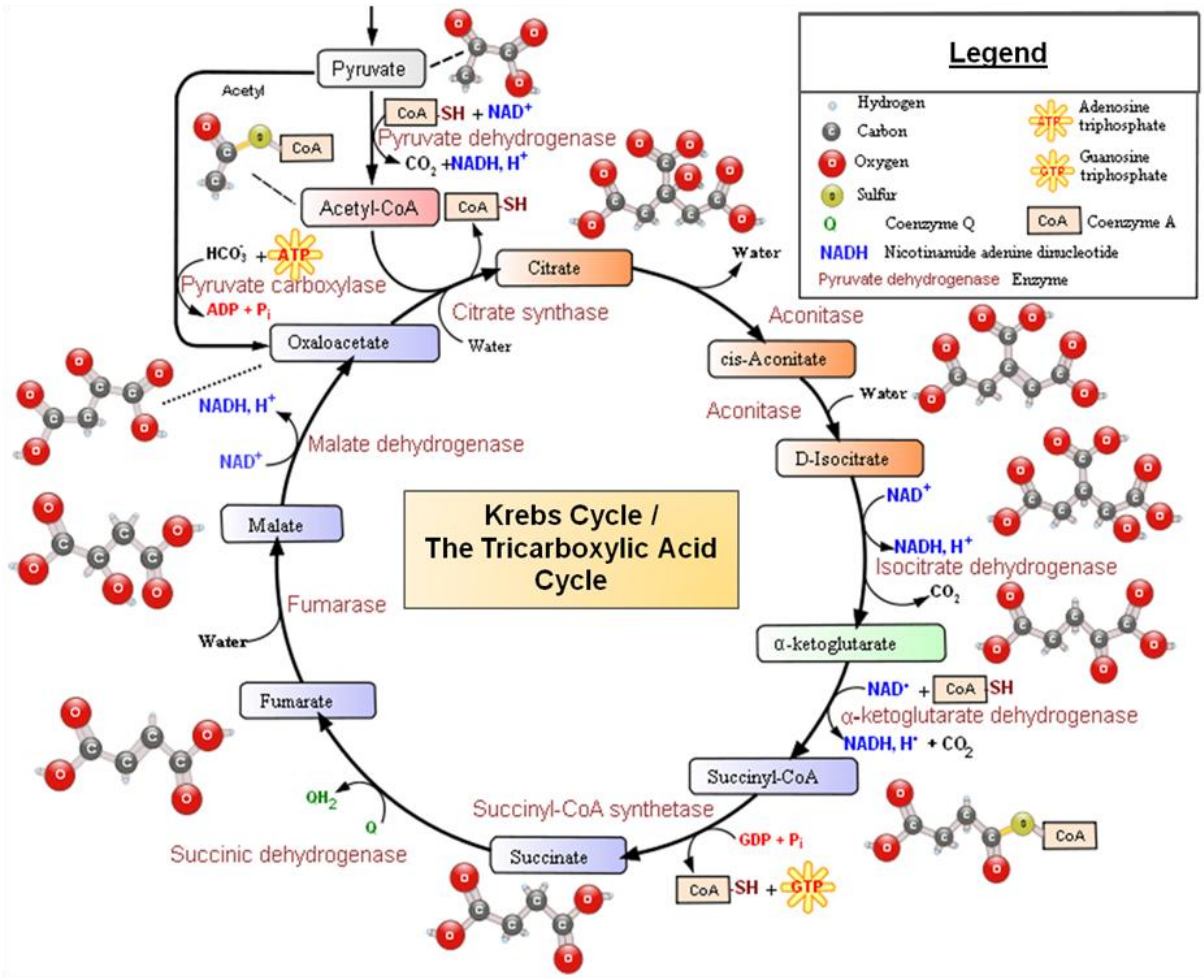

Figure 1.2 A schematic of the tricarboxylic acid / Krebs cycle (Adapted from Mrabet, 2009).

1.2.3 Glucose Metabolism in the Brain

The adult brain utilises glucose at a rate of approximately 5.5 mg/min/100 g (Kennedy and Sokoloff, 1957). The brain has minute stores of glucose in the form of glycogen in glial cells and subsequently relies almost exclusively on provisions from the circulating blood. Unlike in the peripheral tissues (e.g. muscles), uptake of glucose in the brain does not rely on the influence of insulin. Animal studies evaluating intracellular glucose in comparison to brain blood glucose levels, found that intracellular glucose concentration levels were at approximately 25% of that in blood (Mason et al., 1992, McNay and Gold, 1999). In humans brain glucose levels have been found to vary between 20 – 30% of circulating glucose levels, dependent upon the methodology used (Messier, 2004).

Such a discrepancy between glucose concentrations is an important one, as this indicates that glucose is entering the brain via a facilitative mechanism, with glucose utilising a

concentration gradient to facilitate entry into the brain. Diffusing down the gradient allows for faster transportation of glucose from the blood into the brain. A further advantage of facilitative transport is that it does not require energy consumption to act.

Unequivocal evidence of the exact process of glucose metabolism in the brain has not yet been established, however, a prominent theory that has emerged, was first postulated by Pellerin and Magistretti (1994) in Switzerland. Pellerin and Magistretti (1994) refer to an endothelial glial anatomical unit and neuronal unit. Blood glucose crosses the blood-brain barrier via the luminal and abluminal membranes of the endothelial cells, into extracellular space, with the majority taken up by the astrocytes. Here the glucose is metabolised to glycogen (of which the limited stores are located in the astrocytes), or further metabolised through glycolysis to pyruvate, then further to lactate. Whilst astrocytes do posses the capacity to convert pyruvate to acetyl CoA through the TCA cycle, the preference of glial cells is to convert the glucose to pyruvate then lactate as opposed to oxidative metabolism.

According to this model lactate from the astrocytes is then shuttled to the neurons through the monocarboxylic transporter type 1 (MCT1) into the extracellular fluid, and is taken up by the neurons through the monocarboxylic transporter type 2 (MCT2). Once taken up by the neuron the lactate is then oxidised to pyruvate, then CO_2 and water, generating the required ATP via the TCA cycle. This process enables the production of the most energy within the brain at the sites demanding and consuming the most energy, primarily synapse activation in the developed brain. Neurons also posses the ability to metabolise glucose rather than the substrate lactate, and equally astrocytes can metabolise pyruvate. The preference though is for the first stage of glucose metabolism / glycogen breakdown to occur in the astrocytes, with the remainder occurring in the neurons under normal circumstances. A key point to note is that there is no mechanism for ATP exchange between astrocytes and neurons and as such each must supply its own energy (Magistretti et al., 1999). As astrocytes play a vital role in both energy regulation and transmission via ‘mopping up’ excess neurotransmitters at synapses, it is little wonder that the energy consumption of astrocytes is more than double that of neurons (20 as opposed to 8 nmol/mg/min) (Magistretti and Pellerin, 1999).

As previously mentioned, ketones may also be metabolised in the brain during times of Starvation (VanItallie and Nufert, 2003). Ketones enter the neurons via the MCT2, through which lactate also enters. Ketone bodies are metabolised directly by the mitochondria and are eventually metabolised via the TCA cycle, again forming ATP.

As the brain relies upon circulatory provision of its primary energy source, the delivery system for this energy is well evolved, with the brain being a richly vascularised organ. Vast networks of capillaries throughout the brain enable quick responses to changing demands via vasodilatation and constriction of the capillaries enabling increased provision of metabolic resources during increased activation and fuel demand.

1.2.4 Glucoregulation and Glucose Transportation

1.2.4.1 Endocrine Glucoregulation

While the metabolism of glucose both in the brain and the periphery of the body was considered in the previous sections, little consideration has been given to the transportation of glucose or the regulatory processes responsible for maintaining (or failing to maintain) optimum glucose levels in the blood.

Glucoregulation refers to the body's ability to process and maintain glucose levels within the body, in order to adhere to strict glucose homeostasis. The hormones insulin and glucagon are vital in maintaining glucose homeostasis and glucoregulation. Both are secreted from the pancreas, although their effects are opposite. Both insulin and glucagon are secreted from the islets of Langerhans, which is comprised of four cell types (α, β, δ & PP), which release hormones directly into the blood stream. The hormonal feedback of circulating levels allows the accurate modulation of appropriate hormone secretions by the pancreas (in healthy individuals).

Insulin is released by β cells primarily in response to rising blood glucose levels, typically following feeding. Insulin is also released in response to several other stimuli (e.g. neural stimulation via the vagus nerve prior to expected food consumption). Insulin stimulates glycogenolysis, whereby glucose is metabolised through the catabolic metabolic pathway to synthesise glycogen, which is stored in the liver and muscles. In addition to stimulating glucose to be stored, insulin also promotes the use of amino acids in the periphery. This then acts to down regulate gluconeogenesis via the removal of the primary substrate (amino acids) requirement, promoting glycolysis of circulating glucose to meet energy demands. Through several actions, insulin promotes energy storage (as fat in adipose tissue, as protein in muscles and as glycogen in the liver and muscles). The presence of insulin in circulating blood also inhibits the release of glucagon from α cells.

Glucagon has opposing effects to insulin. Glucagon is released in response to falling blood glucose levels. Rather than the net storage of energy, glucagon acts to breakdown glucose and release energy through the anabolic metabolic pathway. The primary action of glucagon is on the liver, a source of easily mobilised glucose from glycogen through glycogenolysis. Following depletion of carbohydrate stores, glucagon acts to release energy through non-glucose substrates via gluconeogenesis, in order to maintain glucose homeostasis. By inhibiting insulin secretion from β cells, glucagon also discontinues storage metabolism. An important feature of glucagon is its signalling to increase lipid metabolism. This releases energy as ketones which can be used in muscles. This in turn decreases peripheral systems dependence of glucose energy supplies, which can subsequently be preserved for the CNS.

Somatostatin is produced by the δ cells and amongst other functions when released inhibits the release of insulin (glucagon inhibits δ cell production of somatostatin). The PP cells secrete polypeptide, which is involved in regulating the endocrine secretion of the pancreas (it is also inhibited by somatostatin and raised glucose levels). Whilst the ratio between insulin and glucagon are the main regulators of blood glucose homeostasis, the hormonal regulation is by no means this simplistic, as (very briefly) indicated by the contributory roles of somatostatin and pancreas polypeptide.

1.2.4.2 Glucose Transportation

The previous section covered the role of insulin and glucagon in glucoregulation. This section is concerned with the transport of glucose molecules into cells both in the periphery and CNS, in order to provide the energy prerequisite for cells. Again glucose transportation is of key importance to maintaining good levels of glucose regulation and homeostasis.

From the small intestine and kidney proximal tubules, glucose is actively transported through sodium dependent glucose co-transporters (SGLT-1 in the intestine, SGLT1 and SGLT-2 in the kidneys). These transporters allow active transport, with glucose molecules transported across the membrane against the glucose gradient (from the intestine into the blood, and to be reabsorbed rather than excreted by the kidneys). This is made possible through sodium gradients. Glucose and sodium are co transported into the cells whereby the glucose concentration rises to the extent it may diffuse out into the blood (Wright et al., 2007).

Insulin facilitates the uptake of glucose into cells, with the exception of the brain and liver which use facilitative diffusion. Facilitative diffusion is useful as it relies on concentration gradients to transport glucose, negating the requirement for insulin and additionally does not require energy to complete. Prime examples include GLUT1, involved in the transport of glucose across the endothelial cells of the blood–brain barrier, and GLUT4, responsible for insulin-stimulated glucose uptake into skeletal muscle (Wright et al., 2007). In muscle and adipose cells the GLUT 4 transporter protein is mediated by insulin. Circulatory insulin following increased glucose levels, binds with insulin receptors on muscle and adipose cells. This in turn initiates several protein cascades (as discussed earlier) and in addition causes the translocation of the GLUT 4 transporter to the plasma membrane. GLUT 4 normally resides in an intracellular membrane compartment, but rapidly populates the plasma membrane in the presence of insulin. This then allows the influx of glucose through facilitative diffusion, whereby the glycogen synthesis etc can occur (McCarthy and Elmendorf, 2007).

Glucose transportation from the blood into neurons remains to be fully determined. At present there are several proposed routes through which glucose is believed to be transported. As previously mentioned, in the brain, facilitative diffusion is key to transporting glucose into the brain, with the brain concentration lower than blood levels (approx 20-30%) (Messier, 2004). Facilitative diffusion of glucose requires transport through biological membranes through specific transport proteins. Glucose requires specific carrier proteins that shuttle glucose across the membranes by GLUT proteins (this occurs at a faster rate than natural diffusion). Fourteen GLUT transporters have been identified, with GLUT 1-4 being known to have distinct roles in glucose homeostasis (Thorens and Mueckler, 2010). At least half of the remaining GLUT transporters to date are not fully understood, with the substrates for them uncertain or unknown, although some are used for other carbohydrates such as fructose (Thorens and Mueckler, 2010).

GLUT 1, 3 and 4 are the most abundant glucose transporters in the brain. GLUT 1 is crucial for transporting glucose across the blood brain barrier through the endothelial cells. Approximately 3-4 times as many GLUT 1 transporters are found on the abluminal (brain side) of the endothethial cells forming capillaries than luminal (Farrell and Pardridge, 1991, Messier, 2004). This bias of GLUT 1 location creates an environment in which glucose is continually able to diffuse from the blood into the brain, by maintaining the higher blood to brain extracellular fluid glucose gradient. Following facilitative diffusion into the endothelial cells, glucose is transported out of the endothelial cells into the brains extracellular fluid. Astrocytes play a key role in neuroregulation and transmission, with

processes that surround capillaries. Close proximity to the capillaries allows the uptake of extracellular glucose into the astrocytes, again by GLUT 1 transporters (Messier, 2004).

GLUT 3 is found on the neurons themselves, and transports glucose from the extracellular fluid into the neuron. GLUT 3 allows direct provision of glucose from the blood (via the endothelial cells and extracellular fluid), to be metabolised in the neuron for energy provision. Alternatively energy is available to the neurons from the astrocytes, which is believed to be primarily transferred as lactate. Lactate is shuttled from the astrocytes by MCT1 into the extracellular fluid, and shuttled into the neuron via MCT2.

1.3 Cognition: The Impact of a Glucose Load

As mentioned in the general introduction, the effect of glucose enhancement on cognition has been widely investigated over the last 25 years. This section will review the findings in various populations, concentrating primarily on the impact on memory as this is the focus of this thesis.

1.3.1 Dose Dependent Effects

Both human and animal studies have found that the widely reported cognitive enhancing properties of glucose are dose dependent, conforming to an inverted U-shaped response curve. Several factors mediate the effect of glucose on memory, including (but not limited to); glucoregulation, age and gender. Such factors also indicate that the dose response of memory to glucose is not uniform across populations, or indeed an individual's lifespan. This section will examine the effective glucose doses that have been shown to elicit enhancing effects in animals and humans, before considering the effect of glucose on cognition across a range of healthy and abnormal populations.

1.3.1.1 Dose ranging studies in animals

Early animal studies found various glucose doses to be effective in moderating memory performance. There appears to be two optimal glucose doses (100 mg/kg and 2 g/kg) that elicit facilitation of performance dependent upon the task being completed. However,

there is evidence that doses as low as 10 mg/kg (Kopf and Baratti, 1996) and as high as 4 g/kg (Messier and Destrade, 1988) can mediate task performance.

In an eight arm maze task, rats completing a working memory task (win-shift, rats receive food only by visiting previously inaccessible arms with no light signals) performance was facilitated by both a 100 mg/kg and a 2 g/kg load (White, 1991). This finding supporting earlier observations of glucose enhancements in rats at these doses (2 g /kg Messier and White, 1987, 100 mg/kg Gold et al., 1986). However, only a 2 g/kg load, but not a 100 mg/kg glucose load, facilitated performance on a memory reference task (win-stay, food was obtained by visiting arms only when a signalling light was on) (Packard and White, 1990). The two versions of the task (win-stay and win-shift) are thought to utilise different brain regions which may account for the differential glucose dose facilitation. The hippocampus is believed to underpin working memory tasks, potentially benefiting from facilitation at both the higher and the lower glucose dose (White, 1991). The caudate nucleus seems to be susceptible to lower glucose doses (White, 1991) and is believed to be intrinsic to learning and memory (Graybiel, 2005).

In a dose response study (using injections of 0, 50, 100, 250, 500, 1000, 2000, 3000 and 4000 mg/kg of glucose), the doses of 100 mg/kg and 2 – 3 g/kg were again shown to be effective in radial maze trials (White, 1991). The interim doses were shown to be ineffective, with the differential dose effects on the win-stay and win shift tasks also replicated (White, 1991). Rodriguez et al. (1994) reported impaired learning following 10, 32, 100 and 2000 mg/kg doses of glucose. A dose of 3.2 mg/kg had no effect but a 320 mg/kg dose enhanced performance. This study did use considerably different methodology (passive avoidance to active avoidance negative transfer paradigm) to those previously discussed here, demonstrating the differing optimal glucose dose dependent upon the task/training being employed

In a further dose response study, rats were administered with an intraperitoneal injection of saline or glucose (0, 100, 250 or 1000 mg/kg), before completing a four armed maze, spontaneous alternation task (Ragozzino et al., 1996). A 250 mg/kg (but not 100 or 1000 mg/kg) dose of glucose increased alternation and also hippocampal acetylcholine release (as measured by microdialysis). Subsequently spatial memory tasks in rats display a dose dependent facilitation response to glucose and are potentially mediated by acetylcholine synthesis in the hippocampus.

While the application of animal studies to human investigation of the glucose effect on memory allows for a great insight into the potential mechanisms, the generalisation of

results is somewhat limited by the small range of tasks and inferred measures from behaviour. Obviously the extrapolation between species raises issues, since the exact mechanisms and processes occurring remain undetermined and may not occur similarly between species. An additional consideration is the timing and method of dose administration. The majority of animal studies utilise post-training injections of glucose (e.g. Kopf and Baratti, 1996, Lee et al., 1988, Okaichi and Okaichi, 1997), whereas the preference in human studies is the less invasive oral glucose load. In human studies of glucose and memory the treatment is also normally consumed prior to task completion rather than during the memory consolidation period.

1.3.1.2 Dose ranging studies in humans

Although glucose loads between 25 g and 75 g have been shown to be effective in facilitating memory in humans, the effective dose is not uniform across all populations. In older adults (with a greater incidence of poorer glucoregulation) a higher end dose of between 50 g to 75 g seems to be the most effective (Messier, 2004). In healthy young adults a lower end dose of 25 g glucose has been shown to be effective in eliciting memory enhancement (Messier, 2004, Sünram-Lea et al., 2010). There is currently very little literature investigating children and adolescents, however, a 25 g glucose load has been shown to be effective in adolescents (13 – 18 yrs) (Smith and Foster, 2008, Smith et al., 2009a, Smith et al., 2009b). There is a clear gap in the literature with regards to any effective glucose dose in younger children, this issue is explored in chapter 2. While the evidence to date suggests that age does appear to be a factor in determining the effective dose of glucose, it should be noted that the dose level is likely to be dependent upon several additional factors including glucoregulatory control.

The reported effective glucose doses (between 25 g and 75 g) correspond to doses of 300 mg/kg to 1 g/kg for a 75 kg human (Messier, 2004). Messier et al. (1998), using a range of doses (10 mg/kg to 1 g/kg) found only 300 mg/kg of glucose to elicit memory facilitation, supporting the considerable body of evidence reporting facilitation of memory by a 25 g glucose load. However, 50 g glucose loads have also been successfully utilised and report facilitating effects in both younger and older populations.

In a dose response study in elderly adults, dosages of 0 g, 10 g, 25 g and 50 g were administered prior to assessment of performance on the Wechsler Logical Memory Test (Parsons and Gold, 1992). In this elderly population, an inverted-U dose response pattern was observed, with optimal glucose enhancement seen following the 25 g glucose drink.

In a dose response study in healthy young adults, dosages of 0 g, 15 g, 25 g, 50 g and 60 g were administered prior to completion of a range of memory tasks (Sünram-Lea et al., 2010). Glucose facilitation effects were observed in this study. However, the effective dosages were not uniform across the memory tasks utilised. This suggests that different mechanisms elicited by glucose at different doses are targeting different aspects of memory, although the specific mechanisms which are responsible remain unclear (see section 1.4 for a discussion of the potential mechanisms). While a 25 g load was observed to facilitate spatial working memory, immediate and delayed free recall and recognition, supporting previous evidence that 25 g is an effective dose in healthy young adults, not all tasks followed the inverted U-shaped dose response curve. Serial three subtractions (numeric working memory) followed a cubic response curve with improvements at both the highest and lowest doses administered. Spatial working memory displayed a quartic trend, with significant improvements following 25 g and trends towards further improvements following 60 g of glucose. These findings indicate that the dose-response function may be dependent on the domain being tested, as opposed to being static across all aspects of cognitive functioning. Further to this, the glycaemic responses to the different glucose doses were seen to be moderated by the glucoregulatory control and body weight of the participant. Such a finding may not be surprising given that increased body weight leads to a decreased dose to body mass ratio, than when consumed by those with smaller body masses. A further issue is that a higher body mass is associated with insulin resistance / poor glucose tolerance (see section 1.3.3.1.1). By definition glucoregulatory control accounts for the body's response to glucose, with poorer glucoregulators seemingly displaying greater evoked glucose levels in response to glucose, which may remain elevated for longer periods. Subsequently similar glucose doses in individuals with different body weights and better/poorer glucoregulatory efficiency leads to differential levels of various physiological responses. For example, Messier et al. (1999) found a 50 g glucose load to be effective in eliciting memory improvements effects in young adults. However, this was seen only in poorer rather than better glucoregulators. Owen et al. (2010) demonstrated a declarative memory benefit in healthy young adults after consumption of a 60 g glucose load, whereas Sünram-Lea et al. (2010) demonstrated such an advantage following the smaller 25 g. The differences between the findings in Owen et al. (2010) and Sünram-Lea et al. (2010), may be in part due to variability of glucoregulatory control within the cohorts tested. Significantly greater blood glucose levels where recorded following 60 g than 25 g in Sünram-Lea et al. (2010), but no significant difference between the two doses were found in Owen et al. (2010).

Consumption of a glucose load has been found to facilitate memory when consumed both prior to task completion, and post task during the consolidation period (In older adults: Manning et al., 1992, In young adults: Sünram-Lea et al., 2002b).

Within the published literature there are no glucose dose ranging response assessments in children. Given that the metabolic rate of the brain in children is up to twice that found in adults (Kennedy and Sokoloff, 1957) and that glucoregulation declines with age, exactly how different doses will impact on cognition in children is unclear. Only three studies to date have administered a glucose drink to children (Benton et al., 1987, Benton and Stevens, 2008, Wesnes et al., 2003), with the majority of studies in children investigating the glycaemic load of breakfasts or snacks on cognition, rather than a pure glucose load. Findings across the limited research to date have been contradictory and are further confounded by the lack of uniform doses across the studies, with both 25 g (Benton et al., 1987, Benton and Stevens, 2008) and 38.3 g (Wesnes et al., 2003) being administered. The time of testing and also dietary restrictions (or lack of) prior to testing also vary considerable between the reported literature. This area and the relevant literature are explored in depth in chapter 2.

1.3.2 Animal Glucose Studies

The glucose enhancement effect was observed in animals in the early 1980's (Gold et al., 1986, Messier and White, 1984). Several tasks were found to be susceptible to glucose manipulations; inhibitory avoidance (Gold, 1986), conditioned suppression (Messier and White, 1987), and appetitive tasks (Messier and Destrade, 1988).

In animal studies of memory, predominantly rats and mice have been used to investigate the modulating effects of glucose administration on memory, although other species such as pigeons have also successfully been utilised (Parkes and White, 2000). Popular tasks employed involve foot shocks in aversive studies, four and eight arm mazes, alternation trials and light association tasks, amongst others. These tasks are common in rodent studies, with the authors interpreting the behaviour of the animals post training as exhibiting learning and memory, to varying degrees dependent upon the behaviours observed.

Studies in animals have administered several different substances to investigate the subsequent effects on memory and learning. Cholinergic agonists have been found to enhance memory, whereas cholinergic antagonists have been reported to impair memory.

Opiate agents on the other hand have the reverse effects, with antagonists enhancing and agonists impairing memory (inhibitory avoidance and spontaneous alternation tests of memory, plus non memory measures such as electrographic sleep, locomotor activity and tremors), which is interpreted to mean that opiates inhibit cholinergic function (Gold, 1991). When studied in conjunction with pharmacological interventions, glucose has been found to exaggerate the enhancing effects of cholinergic agonists and limit the detrimental effects of cholinergic antagonists on a range of memory indices. Glucose has also been shown to counteract the analgesic properties of the opiate morphine in mice (Lux et al., 1988). The authors suggest that this is a direct effect of glucose (and fructose, which also elicited this effect) or their metabolic products within the CNS. It has also been postulated that under certain conditions, circulatory glucose may limit the production of acetylcholine synthesis via the availability of substrate Acetyl-CoA during metabolism. These interactions in animal studies between glucose and opiates / cholinergic function, lend considerable evidence to the theory that glucose is mediating neuronal activity and hence memory via the production of the neurotransmitter acetylcholine. Further, a glucose or adrenaline load (which leads to increased glucose levels) limits the memory deficits induced by scopolamine, which has anticholinergic properties.

Microinjections directly into specific brain regions have been shown to enhance memory and learning (Korol and Gold, 1998). The administration via microinjection of morphine (an opiate agonist) leads to impaired memory in rats. However, by simultaneously administering glucose (or pyruvate), such memory impairments are ameliorated (Korol and Gold, 1998). These findings were observed in several brain areas including the hippocampus and the amygdala. In line with the impairments / facilitation observed, an increased / decreased quantity of the neurotransmitter acetylcholine (measured via microdialysis during learning) was recorded. The quantity of acetylcholine output was also correlated with the memory modulating effect of glucose. This finding supports the postulation that memory modulation may be attributed to the increased synthesis of the neurotransmitter acetylcholine.

Ragozzino et al. (1996) reported increased hippocampal acetylcholine release in a dose dependent response pattern to a peripheral glucose injection, during a spatial learning task in rats. In humans, one potential mechanism for the glucose enhancement effect is believed to the preferential targeting of the hippocampus by glucose administration. The finding that during learning acetylcholine release is increased in this region supports the proposition that increased metabolic resources available to this region in particular may allow greater neurotransmitter synthesis and release. Subsequently, increased neurotransmission activation capacity may account for the memory facilitation observed.

The beneficial effects of glucose administration in animals is believed to be due (to some extent) to the mediation of cholinergic activity in the hippocampus. It has also been suggested that such facilitation may not result solely from acetylcholine modulation via glucose, but may also involve alternative neurotransmitters (including γ-aminobutyric acid (GABA) or glutamate) (Watson and Craft, 2004). Glucose has been shown to reverse the memory and learning impairments induced by opiate and GABA agonists, plus cholinergic and glutamatergic antagonists (Gold, 1995).

Alternative approaches suggest that adrenergic influences are the most likely mechanism through which glucose facilitation is operating (Gold, 1995). Although adrenaline does not cross the blood brain barrier in large amounts (Gold, 1995) its effects on the CNS result in peripheral effects, including increased blood flow and raised circulatory glucose. Glucose administration has been shown to facilitate memory retention when administered both before and after the training in rats (Li et al., 1998). However, when administered following training, this must occur immediately post training. A delay in administering the glucose of only 1 hour is sufficient to negate any enhancements, with performance levels remaining equivalent to that observed in control conditions (Gold, 1991). The timing of the glucose administration here lends support for the adrenaline modulation of memory. When specifically considering the aversive studies employed e.g. with foot shocks administered, glucose levels increase in response to the stress hormones released which are induced by the aversive task. Similar memory and learning effects are observed in response to administration of both glucose and adrenaline (both in terms of timing of administration and displaying an inverted u dose response curve), as measured by avoidance responses made (Gold, 1991). Further, the optimal dose of adrenaline to enhance memory performance on this task, elicited comparable circulatory blood glucose levels to those evoked for the optimal glucose dose on performance (Hall and Gold, 1986, Hall and Gold, 1992). The finding that pre-treatment with adrenergic antagonists blocks subsequent memory facilitation by adrenaline, but not following glucose treatment lends further support (Gold et al., 1986).

There is also a considerable body of evidence which has not demonstrated a glucose memory facilitation effect (e.g. Means and Edmonds, 1998, Messier, 1998, Means et al., 1996). Of the studies which failed to demonstrate facilitation by glucose, several did report an attenuation of deficits by glucose. For example, a slight attenuation of the deficits induced through concurrent administration scopolamine on a water maze alternation task (Means and Edmonds, 1998). However, several of the studies which failed to elicit glucose facilitation, reported that the species of rats used had very good

levels glucoregulation. Circulating glucose levels returned rapidly to baseline levels in Means and Edmonds (1998) study, in which only slight attenuation by glucose of scopolamine was observed. Messier (1998) also reported smaller peak evoked glucose levels in species that were not, as opposed to species that were sensitive to glucose improvements. This infers that glucose modulation of memory may only be effective in individuals with less effective glucoregulatory control whose circulating glucose levels remain elevated for longer periods. This finding is further supported by a rat study reporting a negative correlation between glucoregulation (peak blood glucose and insulin during a tolerance challenge) and performance (memory acquisition during a shock motivated maze task), even though no glucose treatment effect was elicited (Long et al., 1992).

1.3.3 Human Glucose Studies

A plethora of studies have investigated the impact of glucose on cognition in humans over the past 25 plus years. In this section, the evidence from various populations (normal and abnormal) is considered in order to gain an overview of the glucose facilitation effect on memory.

1.3.3.1 Abnormal Populations

Abnormal populations present an opportunity to investigate the effects of glucose on cognition in individuals who would normally present with performance levels lower than that observed in healthy normal participants. The neuro-degeneration and specific neuronal problems that are observed in some abnormal populations, allows interpretations to be drawn as to the specific mechanisms targeted by glucose facilitation. The effect of glucose facilitation has been observed in several abnormal populations. Research has indicated that the enhancement effect elicits a greater facilitation in these normally deficient populations (Messier and Gagnon, 1996). The evidence from such populations is considered in this section.

1.3.3.1.1 Diabetes and the Metabolic Syndrome

Obesity, hypertension, impaired glucose tolerance and dyslipidaemias are a few of the conditions that often present together, and are known as the metabolic syndrome. Insulin resistance is a basic underlying feature in the metabolic syndrome, with sufferers prone to elevated risk of developing diabetes and cardiovascular disease. Over the last 20 years there has been a drastic increase in the incidence of metabolic syndrome. Whilst specific definitions and diagnosis are not yet globally accepted, it has been documented that approximately 25% of the US population currently suffer metabolic syndrome (Cameron et al., 2004, Ford et al., 2002b). Data for the UK prevalence is not available, however, data from Scotland and Ireland are in line with the US populations (Cameron et al., 2004). A consistent finding across the studies is the increased prevalence of metabolic syndrome with age and also with levels of obesity (Eckel et al., 2005). Metabolic syndrome has been associated with reductions in recall, reduced overall intellectual functioning, as well as reductions in learning and executive functioning, all of which were associated with impaired insulin resistance (Hassenstab et al., in press).

There are two types of diabetes. Type 1 is associated with decreased production of insulin, resulting in continually raised glucose levels, requiring the administration of exogenous insulin in order to manage the disease. Where type 1 diabetes develops, it is often present in the early years of a child's life and has been termed juvenile-onset diabetes. Type 2 diabetes on the other hand generally has a later onset, developing over the course of several years. Type 2 diabetics suffer from insulin resistance (through deficits in peripheral insulin signalling and β-cell functioning) which is often a result of a culmination of lifestyle choices (though this type also encompasses gestational diabetes). Type 2 diabetes can often be managed with dietary interventions and can (although not in every case) be non-insulin dependent (Non-Insulin Dependent Diabetes Mellitus [NIDDM])

Poor glycaemic control in type 2 diabetes has been associated with several cognitive impairments (Awad et al., 2004), including poorer declarative memory performance (Greenwood et al., 2003, Strachan et al., 1997). Improving the glycaemic control in diabetic patients through the use of drug interventions, has been shown to lead to a corresponding improvement in memory tasks (Ryan, 2006). This improvement suggests that poor glucoregulatory control in diabetics is (at least in part) contributing to the measurable decrements in cognition observed. In type 1 diabetes cognitive deficits are seemingly characterised by reduced mental speed and flexibility (Brands et al., 2005), particularly during periods of hypoglycaemia (Gold, 1995). A number of studies have investigated the impact of diabetes on cognition (Messier et al., 2004, Messier and

Gagnon, 1996). A wide range of impairments have been observed but include verbal declarative memory, visuo-spatial memory and selective attention (Messier et al., 1999). Overall however, the studies to date concur that the majority of diabetic patients suffer impairments in verbal memory and that these impairments worsen with age and duration of the disease (Elias et al., 1997, Fontbonne et al., 2001, Grodstein et al., 2001, Ryan and Geckle, 2000, Stewart and Liolitsa, 1999, Strachan et al., 1997).

A limitation when considering those with diabetes or metabolic syndrome is the co-presentation of additional damage e.g. cerebrovascular and cardiovascular damage (Messier, 2003). Risk factors for diabetes also include obesity, hypertension and high cholesterol, which have independently been shown to be associated with cognitive impairments (Lamport et al., 2009). Such damage may act in conjunction with or independently of any effects seen following glucose administration. Subsequently it is not always possible to determine the causality of the impairments identified.

1.3.3.1.2 Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disease, presenting with progressively deteriorating brain functions including; memory, understanding, judgement, language and thinking (Luengo-Fernandes et al., 2010). AD is the most common form of dementia, accounting for ~60% of dementia cases in the UK which equates to approximately 500,000 suffers. Dementia is most prevalent in people over 65 years (late onset), although young onset dementia is also found. With the ageing population, the number of sufferers is predicted to rise further with estimates in the region of 1,041,000 by 2051 (Knapp et al., 2007). No definitive cause for AD onset has been discovered, however, several features and risk factors of the disease have been identified.

Many patients presenting with AD also display impaired glucose tolerance, specifically in the form of insulin resistance (Messier, 2003). AD patients displayed higher insulin concentration in response to glucose administration and reduced insulin mediated glucose uptake when compared to matched controls (Craft and Watson, 2004). Interestingly this glucose dysregulation has been found to be present during the early stages of AD and is characteristic of AD suffers who do not possess the apolipoprotein E Є4 allele (APOE Є4), an established risk factor for AD (Craft et al., 2003). Several risk factors for AD have been identified of which abnormal glucose metabolism is one key feature (others include abnormal lipid metabolism, oxidative stress, inactive lifestyles, obesity, type II diabetes and decreased cerebral blood flow) (Martins et al., 2006). Whilst diabetes is believed to

account for a small increase in the risk for developing AD, this risk is considerably larger in diabetic patients displaying cerebrovascular disease. This finding suggests that cerebrovascular disease may be mediating the risk for developing AD (Messier, 2003). Cerebral metabolism deficits are evident in AD, which reflect the neuro-degeneration within this disease. Position Emission Tomography (PET) studies have demonstrated the decrements in brain glucose metabolism in AD patients when compared to matched controls (Duara et al., 1986, Kuhl et al., 1985).

A key feature of AD is the behavioural impairments stemming from cholinergic degeneration, which occurs principally in the basal forebrain (which projects to the hippocampal formation) (Watson and Craft, 2004). Subsequently decreased activation and cell death in this area may have considerable repercussions on memory functioning. As modulation of cholinergic processes in the brain is one potential mechanism responsible for the glucose memory enhancement (see section 1.4), this population is of particular interest. Should glucose mediate memory processes via modulation of cholinergic activity, it may be predicted that suffers of Alzheimer's disease may be particularly susceptible to the glucose memory enhancement effect. Indeed there are several studies which have reported facilitation following glucose ingestion in participants with AD or suspected AD (Craft et al., 1992, Manning et al., 1993)

Several studies have suggested a link between memory and blood glucose levels in AD (Duara et al., 1986, Kuhl et al., 1985, Meneilly and Hill, 1993). In patients with probable AD, a glucose load has been shown to deliver facilitation in performance on several aspects of cognition; orientation, narrative prose, face recognition, word recognition and recall (Manning et al., 1993). Glucose facilitation has also been shown to be effective in both AD and matched controls, however, the facilitation presented differently in the different populations (Craft et al., 1992). Normal controls displaying better glucoregulation (indicated by better recovery time to base blood glucose levels), were facilitated by glucose when completing a paragraph recall task, whereas poorer regulators were impaired. This pattern was reversed in AD, with facilitation seen in poorer glucoregulators and impairment in better regulators (Craft et al., 1992). These studies in patients with AD (Craft et al., 1992, Manning et al., 1993) provide supporting evidence that memory is mediated by glucoregulatory processes, particularly in individuals with reduced brain glucose metabolism.

1.3.3.1.3 Down's Syndrome

Down's syndrome (DS) is a genetic disorder caused by the presence of an extra copy of chromosome 21 (or part of). DS is associated with distinctive physical features, cognitive impairments and often mental retardation (Manning et al., 1998a). DS associated impairments include impaired language and memory deficit (both long and short term) (Brown, 1974, Haxby, 1989). By the age of 35 years adults with DS often develop the amyloid plaques and neurofibrillary tangles throughout the cortex, and in the hippocampal structures. The pattern and location of the plaques and tangles in DS are characteristic of those seen in patients presenting with AD (Murphy and Ellis, 1991). In DS these plaques and tangles occur in almost all DS individuals over the age of 35 years, however, only 30% meet the criteria for dementia (Manning et al., 1998a, Schapiro et al., 1987). Brain atrophy and decreased brain metabolic function as measured by glucose metabolism in elderly DS individuals (middle age is considered elderly for DS), also mirror the neuropathology observed in AD (Schapiro et al., 1987).

Research investigating the impact of glucose load on cognition in DS is currently very limited, although due to the similarities between DS symptoms and AD it may be expected that similar findings would occur. In a study of healthy DS participants (mean age 35 yrs, range 19-55 yrs, with participants meeting the criteria for dementia excluded), glucose was found to facilitate long term memory in a DS appropriate test battery (Manning et al., 1998a). Glucose was also found to enhance short and long term word recall, orientation and object location and language abilities along with several other tasks. Improvements on such a wide range of tasks suggest that glucose can act on various neural systems which are responsible for a wide range of function (Manning et al., 1998a). Although these wide ranging indicators of glucose facilitation may be limited to populations presenting with considerable deficits and possibly impaired glucose metabolism.

1.3.3.1.4 Schizophrenia

Schizophrenia is a neuropsychiatric disorder which is characterised by psychosis. In addition to displaying abnormalities in the perception of reality, schizophrenic patients also display cognitive impairments. These impairments include deficits in learning and memory (Gruzelier et al., 1988), attention and in executive functions (Goldberg et al., 1987, Seidman et al., 1991). The most persistent of these deficits, which is also found to be the most resistant to treatment improvements, is long-term declarative memory (Stone et al., 2003). Schizophrenics are also at greater risk of obesity, diabetes, lipid

abnormalities and cardiovascular disorders. The metabolic complications in schizophrenic patients are associated with several risk factors including: family history, lifestyle, smoking, dietary habits, physical inactivity, but also with antipsychotic medication (Maric et al., 2008). Consequently impaired glucose tolerance is a common feature of schizophrenia, with the ensuing hyperglycaemia being associated with insulin resistance and potentially contributing to the cognitive impairments suffered (Schultz et al., 1999).

Following a 50 g glucose load, verbal declarative memory on a paragraph recall task was found to be enhanced relative to placebo in schizophrenics (Newcomer et al., 1999). This finding was not replicated in control subjects (normal or bipolar affective) whose glucoregulatory control was not compromised (Newcomer et al., 1999). A dose response study by the same group (Fucetola et al., 1999) revealed that schizophrenic patients demonstrated higher levels of evoked circulatory glucose and insulin responses than control subjects following the same glucose treatments. Older schizophrenics displayed dose dependent memory enhancements in a spatial task in response to glucose whereas a 75 g load impaired attention in younger schizophrenics.

Verbal declarative memory was also shown to be enhanced by glucose administration by Stone et al. (2003), who also reported vigilance impairments. Following this the authors demonstrated, using functional Magnetic Resonance Imaging (fMRI), that during encoding of novel information, schizophrenics displayed increased activation of the left parahippocampus having consumed 50 g glucose rather than placebo (Stone et al., 2005). A further trend indicated that left dorsolateral prefrontal cortex was targeted by glucose. However, in spite of the increased activation observed, no memory enhancements were recorded. These findings reiterate the importance of not only the medial temporal structures during the encoding phase of memory, but also the potentially influential role of the prefrontal cortex.

1.3.3.2 Healthy Populations

1.3.3.2.1 Children and Adolescents

Evidence from studies investigating the potential glucose facilitation of memory and other cognitions in children and adolescents is at present limited. However, a small body of work has been published investigating the adolescent population by Smith and colleagues. In adolescents 25 g of glucose was found to facilitate recognition memory in

adolescents (13-18 yrs), with glucose also speeding response times during the recognition task (Smith et al., 2009b). Glucose also facilitated short and long delayed recall plus delayed cued recall in adolescents (14-17 yrs) replicating glucose facilitation findings in young adults of verbal declarative memory facilitation under divided attention conditions (Smith and Foster, 2008). Verbal episodic memory was also enhanced at recall and following a week long delay by anterograde glucose administration in adolescent males (14-17 yrs) (Smith et al., in press). It should be noted that these studies were not double blind, with no taste masking agent added to the treatments in order to disguise the contents (which were otherwise matched for sweetness), introducing potential confounding implications for the results reported.

Whilst a wealth of studies have investigated breakfast, glycaemic loading and snacks on the cognition of children (e.g. Benton et al., 2007, Ingwersen et al., 2007, Micha et al., 2006, Micha et al., 2007), there are limited studies which have administered a pure glucose treatment in drink form as per the adult studies. Those that have administered the glucose drinks have revealed conflicting evidence with regards to the impact of glucose on cognition. In 6-7 year olds, glucose was found to speed reaction times during a sustained attention task and decrease frustration in class (Benton et al., 1987). This finding was not replicated in 9-10 year olds with glucose failing to speed reaction times during the same sustained attention paradigm, although 'in class' observation did reveal increased time spent on task (Benton and Stevens, 2008). Benton and Stevens (2008) also found limited evidence for picture memory facilitation. Contrary to these findings, 9-16 year olds failed to demonstrate any glucose facilitation during memory and attention tasks, instead displaying performance impairments relative to the control (Wesnes et al., 2003). The methodology, treatments administered and age groups tested in these studies do vary considerably, however, the contradictions reported are still somewhat surprising. These studies and their implications are reviewed in detail in chapter 2.

1.3.3.2.2 Young Adults

Glucose has been found to facilitate cognitive performance on a number of tasks in healthy young adults, although not all aspects of performance are facilitated. Often the effects observed on susceptible measures provide inconsistent findings of glucose facilitation. These inconsistent findings are somewhat explained by the wide range of methodologies (and indeed treatment content) employed across the literature.

Hall et al. (1989) report glucose facilitation of digit span but not paired associate delayed recall, logical memory or immediate spatial memory. However, Hall et al. (1989) administered a 50 g glucose load, which has been found to be more effective in older adults, rather the lower 25 g dose which appears to be a more effective dose for younger adults (Riby, 2004). The choice of dose here may account for the lack of memory facilitation observed. Craft et al. (1994) however, reported enhancements at delayed recall for the paragraph recall test, but not on other memory measures (procedural, working and verbal fluency). Spatial memory improvements were observed in several studies reported by Sünram-Leas group (Sünram-Lea et al., 2002a, Sünram-Lea et al., 2001). Improved facial recognition (overall rather than feature specific) has also been shown to be elicited following a glucose load in young adults (Owen et al., 2010, Metzger, 2000, Metzger and Flint, 2003). A 60 g glucose load (but not a 25 g load) was found to enhance implicit memory (Owen et al., 2010). With glucose also shown to facilitate paired associates learning in young adults (Riby et al., 2006).

The most reliable area of cognitive performance to reveal glucose facilitation among healthy young adults is declarative memory. These tasks require the explicit recall of previously displayed materials or events. Word recall tasks are both easy to administer and analyse, as such they are often employed in various forms throughout the glucose literature. These task have repeatedly displayed a glucose facilitation in performance across a number of studies, with such findings now considered to be robust (Messier, 2004). Having stated that the finding is robust, it should also be noted that several studies also report no effects of glucose on memory (Hoyland et al., 2008, Riby, 2004) and it is possible that studies failing to demonstrate the effect may not be as readily published, potentially biasing the literature.

Several studies have failed to find the well accepted glucose facilitation effect on declarative memory. Scholey et al. (2001) reported no significant effect of glucose (25 g) on word memory in healthy young adults, although a trend for increased word retrieval during a verbal fluency task was observed. The trend for a glucose effect on verbal fluency was previously reported by Kennedy and Scholey (2000), suggesting that while the glucose effect may be small it may be consistent within this task. Again no glucose facilitation of word recall or recognition was observed during a study manipulating the emotionality of stimuli (Ford et al., 2002a), with glucose not enhancing emotional material that benefits from natural emotionality enhancements (Brandt et al., 2006). A glucose load (37.5 g) failed to exert any significant effects on word recall, word recognition or picture recognition (in addition to further measures of attention and reaction time) (Scholey and Kennedy, 2004). No glucose enhancement of recognition memory was

observed by Scholey et al. (2009a), although glucose effects were observed on a co-completed secondary task. No effect on verbal recall or recognition scores were found by Green et al. (2001), although glucose (50 g) was seen to improve word recognition speeds (It should also be noted that this study administered 500 ml treatments, a considerably greater volume than that usually administered (200-330 ml). During a low effort task glucose (25 g) was not found to facilitate word recall (Sünram-Lea et al., 2002a), although during a divided attention dual task glucose was able to elicit a beneficial effect. The finding of glucose facilitation being mediated by task demand is considered in depth in section 1.3.5.

The facilitation of memory in young adults has tended to be detected in tasks which have divided attention or induced considerable cognitive demands following glucose consumption. For example when low imagery and /or longer stimuli lists are utilised (Meikle et al., 2005), or when encoding of verbal memory stimuli takes place concurrently with a secondary motor task (Foster et al., 1998, Sünram-Lea et al., 2002a, Sünram-Lea et al., 2001, Sünram-Lea et al., 2002b, Sünram-Lea et al., 2004). However, increasing cognitive demand does not automatically exaggerate any pre-existing glucose facilitation effects (Riby et al., 2006).

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Word recall (immediate and delayed), and word recognition have been relatively consistently enhanced, following hyperglycaemia subsequent to a (25 g) glucose load in young adults (Benton et al., 1994, Foster et al., 1998, Meikle et al., 2005, Sünram-Lea et al., 2001, Sünram-Lea et al., 2008). In this population a (25 g) glucose drink has been shown to enhance verbal declarative memory following both anterograde and retrograde administration of glucose to stimuli display (Sünram-Lea et al., 2002b). However, in the case of retrograde administration, this must be immediately following stimuli display as even small delays ameliorate the glucose enhancement. This suggests that glucose may not solely be influencing memory at encoding, but also during other stages of memory.

Glucose has also been found to enhance performance in young adults at time points both during the morning and afternoon (Sünram-Lea et al., 2001). Though perhaps this is not surprising given the declining glucoregulation observed throughout the day in line with circadian rhythm (Van Cauter et al., 1997). The preservation of glucose facilitation on memory in the afternoon may not be mediated by the same processes as those observed in the morning, but may actually be due to poorer glucoregulatory control over the afternoon. Additionally, while the majority of studies have utilised over night fasting protocols, glucose facilitation has been observed following a more naturalistic 2 hour fasting period (Sünram-Lea et al., 2001). The benefit of testing throughout the day and

following shorter fasting periods is twofold a) more participants may be tested in a larger time window and b) shorter fasting periods are less uncomfortable for participants, potentially aiding compliance and allowing for a representation of the effect of glucose on cognition in participants presenting in a more natural homeostasis state. However, the draw backs to these methodologies are considerable. Lack of dietary restrictions may allow for alternative uncontrolled compounds to be acting on cognition during the testing period, for example caffeine or the secondary meal effect. The secondary meal effect refers to the influence of the glycaemic index (GI) an evening meal on the glycaemic response to breakfast the following morning (Wolever et al., 1988). For example a high GI evening meal, evokes a greater glucose and insulin response to breakfast the following day (Stevenson et al., 2008, Stevenson et al., 2005). Additionally hormonal fluctuations in line with the circadian rhythm may also be influential in cognitive performance.

1.3.3.2.3 Ageing Populations

Memory declines with age (Gold, 1991, Hasher et al., 1989, Zacks et al., 2000, Zacks et al., 1996). Episodic / declarative memory seems to be particularly susceptible to decrements in line with age (Zacks et al., 2000). Declining memory with age is found in both human and animal subjects (Korol and Gold, 1998). In parallel with this, is the finding that glucose facilitates greater and arguably more consistent memory enhancements in elderly populations (Hall et al., 1989, Messier, 2004, Riby et al., 2009, Riby et al., 2006, Riby et al., 2004b). It should be noted, however, in light of the varying methodologies employed across studies, firm conclusions are difficult to draw. A meta-analysis failed to provide evidence that glucose does elicit greater cognitive benefits in older rather than younger adults (Riby, 2004).

An early study (Hall et al., 1989) investigated the effect of glucose on the memory of a healthy ageing human population (mean age 67.3 yrs), using the Weschler Memory Scale. Performance following glucose (50 g) was enhanced when compared to a saccharin placebo, primarily on the logical memory test. These findings have been replicated (Manning et al., 1990, Manning et al., 1997, Manning et al., 1992), with the verbal declarative tasks also facilitated by glucose, although attention, motor function and overall cognitive performance were not altered through glucose administration. Glucose tolerance was also shown to be predictive of performance during the declarative memory tasks (Manning et al., 1990). The increased susceptibility of older participants has since been replicated and reported in several studies.

Healthy older adults have shown glucose facilitation during paragraph recall (Craft et al., 1994, Gonderfrederick et al., 1987, Hall et al., 1989), delayed spatial memory, verbal and figural fluency (Allen et al., 1996). In elderly subjects a glucose load was found to enhance memory during a paragraph recall task when administered both prior to and immediately subsequently to the acquisition period (Manning et al., 1992, Manning et al., 1998b). However, no such facilitation was observed on procedural, working memory or verbal fluency (Craft et al., 1994), highlighting the contradictions to be found amongst the literature.

Episodic memory was found to be enhanced following a 25 g glucose load in elderly adults following an unrelated paired associates task, particularly during immediate recall (Riby et al., 2004b). Riby et al. (2006) however, failed to find evidence of an age effect on glucose facilitation using a similar task when comparing elderly and young adults. The authors suggest that the lack of an age effect may be due to insufficient additional metabolic resources being made available to elderly participants, as a 25 g glucose load was given to both young and elderly participants. Evidence has suggested that a 50 g load is a more effective dose in older adults (Manning et al., 1998b, Messier, 2004). Although earlier studies indicated that a 25 g load led to optimal memory enhancement in elderly adults (Parsons and Gold, 1992). It is possible that the effects following a 25 g load in the elderly are small and subsequently were not detected in Riby et al. (2006) who's elderly sample consisted of 13 participants as opposed to the 20 utilised in Riby et al. (2004b).

A key feature of ageing is declining glucoregulatory control (Messier and Gagnon, 1996). Poorer memory task scores (Weschler composite, logical memory and verbal selective reminding scores) were found with greater peak glucose levels following glucose treatment in the elderly (Hall et al., 1989, Manning et al., 1990). This negative correlation was also representative of performance on these tasks following saccharine placebo. However, these correlations were not evident when examining the data from young participants. This gave one of the first indications that glucoregulatory control may mediate cognitive performance, selectively in older adults (Hall et al., 1989). Support for such glucoregulatory dependent cognitive decline was reported by Perlmuter et al. (1984) and Perlmuter et al. (1987). Perlmuter et al. compared matched elderly diabetic and non-diabetic participants, and found that memory impairments were greater in the diabetic population. Whilst this finding at the time was remarkable, the physiology behind diabetes has been investigated intensely over the last 2 decades. We now know that diabetes does not simply impair glucoregulatory control, but also induces a wide range of damage. For example cerebral-cardiovascular damage, cholesterol, hypertension etc.

Subsequently it may not be possible to wholly attribute the cognitive deficits in elderly diabetics (whose disease duration is unknown) purely due to glucoregulatory deficits of glucose, but may be a result of the composition of additional damage sustained over the course of the disease.

There are a number of possibilities that explain these deficits in memory and learning in ageing. Deficits in the brains integral neuronal structural (neuron structure, chemical or conductivity of neurons) and / or deficiencies in regulatory mechanisms that modulate memory and learning may occur with ageing (Korol and Gold, 1998). The particular susceptibility to glucose facilitation in older adults suggests that deficits in the regulatory mechanisms within the brain are likely to be responsible for this decline. Riby (2004) highlighted that research pertaining to the glucose effects in older adults should be treated with caution. Firstly, the scope and quantity of research examining glucose and cognition in this population to date is limited. Additionally, in older adults there is a large variability in the glucoregulatory control that older participants present with. The decline in cognition and glucoregulatory control are features which make this population interesting to examine. However, failing to accurately assess glucoregulatory control may lead to potential effects on cognitive performance being missed.

1.3.4 Cognition and Glucoregulation

A link between an individual's level of glucoregulatory control and cognitive functioning has now been well established (Awad et al., 2002, Messier, 2005, Riby et al., 2004b, Wenk, 1989). Populations which present with poorer glucoregulatory control have been suggested to be the most susceptible to a) cognitive impairments and b) facilitation following hyperglycaemia induced by a glucose load. Decrements in verbal memory (logical memory but also immediate and delayed memory) seem to be the most strongly resultant deficits associated with poor glucose tolerance (Lamport et al., 2009).

One appealing account for a greater beneficial effect on cognition in poor glucoregulators is the resultant greater increases in blood glucose levels which are also maintained for longer periods than in better glucoregulators (Awad et al., 2002). However, there remains contradictory evidence in the literature and it is worthwhile to consider research which has assessed healthy young and healthy ageing populations, since ageing is associated with declining glucoregulatory control. For example in older adults, the glucose memory facilitation effect has been shown to be more pronounced in those individuals exhibiting better glucoregulation as opposed to poorer (Craft et al., 1994, Meikle et al., 2004,

Messier et al., 1997). In healthy adolescents better rather than poorer regulators have been found to display glucose facilitation of memory (Smith and Foster, 2008). Younger adults with poorer glucoregulation have also been shown to be more susceptible to the glucose attenuation than better regulators (Awad et al., 2002, Messier et al., 1999). Poorer regulators in abnormal populations presenting with poorer glucoregulation have also demonstrated beneficial effects of glucose on cognition e.g. DS, Schizophrenia and AD (Fucetola et al., 1999, Manning et al., 1993, Manning et al., 1998a, Stone and Seidman, 2008, Stone et al., 2003). In older adults with mild cognitive impairments glucoregulatory indices have been shown to be predictive of subsequent memory performance (Riby et al., 2009). Supporting this are studies reporting older poorer regulators to be more susceptible to glucose facilitation than better regulators (generally of attenuation of deficits rather than enhancements per se) (Hall et al., 1989, Kaplan et al., 2000, Messier et al., 2003). Given this wealth of evidence across numerous populations, it seems somewhat unlikely that the co presentation of cognitive impairments and poor glucoregulation is coincidental, but the interaction on memory following a glucose load remains to be fully understood.

Assessment of glucoregulation via a 75 g oral glucose tolerance test (OGTT) following an overnight fast is the gold standard. By taking measurements of circulatory blood glucose at baseline and several points over a 2 hour post-dose period, an overview of an individual's glucoregulatory response to glucose can be obtained. The change in glucose levels at various points enables an overview of several aspects of glucoregulatory control (e.g. area under curve (AUC), time of and peak evoked glucose levels, recovery time to baseline, etc) and is used for diagnostic purposes within clinical settings. For clinical diagnosis, baseline blood glucose and levels 2 hours post dose are the most common aspects used for assessing fasting glucose, impaired glucose tolerance and diabetes. Using this technique, both Awad et al. (2002) and Messier et al. (2003) were able to correlate several aspects of the 75 g dose response curve with cognitive functions, although both studies used differing specific indices of the OGTT. In young adults, Awad et al. (2002) reported better glucoregulation as determined by a) faster recovery to baseline OGTT levels and b) lower peak evoked blood glucose values being associated with better performance on several verbal declarative measures (immediate and delayed paragraph recall, plus verbal free recall). Higher blood glucose in response to the OGTT was associated with poorer glucoregulation and poorer performance on memory tasks.

Messier et al. (2003) observed in older participants (55-84 yrs) several correlations between blood glucose measures of glucoregulatory control and performance on cognitive tasks, with limited correlations observed for cognition with insulin (c-peptide) responses.

Messier et al. (2003) observed that similar correlations were observed with task performance following saccharine, but that these relationships were modified by the administration of glucose. Following consumption of saccharin, better glucoregulators were seen to perform better than poorer e.g. on the digit span task (forward), however, this difference was ameliorated following glucose consumption. The older poorer regulators performed worse than better regulators on several tasks of working memory, verbal memory and executive functions. Administration of glucose to this group seemingly enhanced performance on all but the executive functions task (Modified Brown-Peterson). This finding supports the postulation that glucose differentially interacts with cognition dependent upon the initial glucoregulatory control status. Whilst enhancements in performance were not observed, facilitation in the form of glucose obliterating the performance differences between glucoregulators was.

Research investigating the cognitive functioning in individual with impaired glucose tolerance as characterised by impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) has not however, provided definitive evidence. A recent review (Lamport et al., 2009) reported that there is little evidence of an association between IFG and IGT. However, Lamport et al. (2009) also highlight the issue that the standardised tasks utilised in these studies (such as the Mini Mental State Exam (MMSE) and the Wechser Adult Intelligence Scale (WAIS) are unlikely to have been sufficiently demanding / sensitive enough to detect any subtle cognitive performance deficits in these populations. The level of demand induced by cognitive demand is pivotal in uncovering any subtle performance decrements, as covered in depth in section 1.3.5.

Poorer glucoregulation in healthy non-diabetic elderly (72 yrs to 84 yrs) participants have been shown to display worse performance in working memory, verbal declarative memory and executive functions, when compared to similar better glucoregulators (Messier et al., 2003). A glucose load (50 g) was found to attenuate this decrement, lessening the magnitude of impairments observed for working and verbal memory, when compared to better glucoregulators (Messier et al., 2003). This finding was also observed in a healthy young sample with glucose dose (50 g) reversing the poorer memory performance observed in poorer glucoregulators after saccharine consumption (Messier et al., 1999). In older adults similar cognitive impairments (logical memory, free recall and recognition) were again observed in male (but not female) poorer glucoregulators, however, a glucose load (50 g) was shown to facilitate memory in better male glucoregulators whilst impairing poorer regulators (Messier et al., 1997).

Craft et al. (1994) compared older (mean age 68.5 yrs) and younger (mean 20.8 yrs) adults to reveal opposite effects in the young compared to elderly. A glucose load (50 g) was found to enhance memory in young poorer glucoregulators but inhibit the memory in better glucoregulators. However, glucose has no measurable effect on older poorer regulators whilst enhancing older better glucoregulators memory performance. It has been suggested that glucose effects may be more readily observed in younger adults with poorer glucoregulation, due to the increased periods of raised blood glucose levels. This allows for an extended time period in which glucose levels are raised and a memory enhancing effect may be exerted (Craft et al., 1994). As glucoregulation declines with ageing, it may be that the glucoregulatory indices in better older regulators are more in line with those observed in younger poorer regulators, allowing for similar memory effects to be observed. Consequently the glucose dose administered may be simply fail to raise circulatory levels sufficiently to ameliorate decrements observed in the poorer older regulators.

The interaction between glucose administration, cognitive facilitation and glucoregulatory control however, remains to be fully disentangled. The evidence to date, in populations presenting within the normal glucose tolerance range highlights the contradictory nature of the facilitation effect of glucose in better and poorer glucoregulators. There are contradictions within the literature as to whether better or poorer glucoregulators benefit from cognitive enhancement following a glucose load. Such contradictions may indicate that in studies which fail to take into account glucoregulatory effects, any potential glucose effects may be being cancelled out and subsequently missed, accounting for the null findings.

Consequently the examination of the potential interaction between glucoregulation and cognition across a range of supposedly (self report) healthy individuals may allow valuable insights as to any early memory impairments which may present in normal individuals. A considerable advantage of examining individuals in the early stages of glucose tolerance decline, but within normal ranges, enables the considerations of glucoregulation without the confounds of cerebrovascular disease that is often associated with poor glucoregulation in unhealthy / ageing / abnormal populations.

This thesis is primarily concerned with the impact of glucose and glucoregulation on memory in healthy young adults, who have not been diagnosed with any metabolic disorders. Several studies within the glucose literature have assessed glucoregulation within this population whilst assessing the effect of a glucose load on cognition, however, this has primarily been a secondary aim of such studies. In contrast to this, the impact of

glucoregulation on memory is primary consideration within the memory paradigms assessed within this thesis. Specifically in chapter 3 with methodological improvements made to the assessment of glucoregulation employed in chapters 4, 5 and 6.

1.3.5 Glucose and Cognitive Demand

Whilst the majority of evidence considering glucose facilitation to date has focussed on memory, there is increasing evidence that glucose can mediate performance on other tasks; kinaesthetic movements (Scholey and Fowles, 2002), visual memory (Sünram-Lea et al., 2001), reaction times (Owens and Benton, 1994), the Stroop test (Benton et al., 1994) and psychomotor tracking (Scholey et al., 2009a) amongst others. An interesting discovery which came about through investigation of these alternative tasks is the influence of glucose facilitation on performance during tasks / situations which impose increased demand.

There are a variety of approaches which have elicited glucose facilitation during periods of increased mental effort. Studies have utilised prolonged periods of repeated completions of demanding tasks to create sustained cognitive demand (Kennedy and Scholey, 2000, Owens et al., 1997, Scholey et al., 2001, Scholey et al., 2006) or employed dual tasks, dividing attentional resources and increasing cognitive loading (Foster et al., 1998, Scholey et al., 2009b, Scholey et al., 2009a, Sünram-Lea et al., 2002a, Sünram-Lea et al., 2001, Sünram-Lea et al., 2002b, Sünram-Lea et al., 2004). Alternative approaches have manipulated the difficulty of the stimulus during the tasks (e.g. Meikle et al., 2005).

Donohoe and Benton (1999b) suggested that the level of cognitive demand was critical when investigating the influence of an exogenous rise in circulatory glucose levels on tasks. By increasing the relative level of task difficulty, brain activity and its subsequent metabolic demand are also increased. One mechanism by which glucose may be facilitating performance is by eliminating localised rate-limiting energy deficits in the brain which may in turn limit performance. In support of this, several demanding tasks have been shown to decrease levels of peripheral circulatory glucose levels post test compared to a pre-test levels. Incongruent Stroop, Rapid Information Processing and a difficult computerised ‘tennis’ videogame (pong) were all found to decrease circulating glucose levels and additionally feelings of being ‘energetic’ (Owens et al., 1997). A demanding dichotic listening task also demonstrated a fall in circulatory glucose following a glucose load (Parker and Benton, 1995). Fairclough and Houston (2004) observed greater decreases in glucose levels following an extended period of completing incongruent rather

than the easier congruent Stroop, even though no glucose load was administered. Compared to a finger tapping control, completing a demanding serial sevens subtractions over an extended period (5 min as opposed to the more standard 2 min application) lead to a reduction in blood glucose (Scholey et al., 2001), with glucose also shown to facilitate performance on this task but not the lesser demanding tasks (Kennedy and Scholey, 2000, Scholey et al., 2001). The reported glucose facilitation, in conjunction with detectable drops in circulatory levels has been demonstrated across several studies. This lends credible support to the suggestion that glucose facilitation occurs in response to demanding tasks (further potential mechanisms are discussed in section 1.4).

Glucose reliably enhances cognitive functioning in healthy young adults during conditions of divided attention at encoding e.g. when encoding of verbal memory stimuli takes place concurrently with a secondary motor task (Foster et al., 1998, Sünram-Lea et al., 2002a, Sünram-Lea et al., 2001, Sünram-Lea et al., 2002b, Sünram-Lea et al., 2004). Healthy adolescents too have shown glucose facilitation of verbal episodic memory under dual task encoding (Smith and Foster, 2008, Smith et al., 2009b).

A common divided attention manipulation completed simultaneously by the participants while encoding the stimuli, is a hand movement task. Participants are required to perform two sets of hand movements, alternating between the two motor sequences after every four completions. This task is particularly demanding as the participants must complete the correct sequence whilst monitoring the displayed stimuli and tracking how many completions of the current sequence have been completed. Using this task to divide attention and increase task difficulty has proven to be very successful in enabling glucose has facilitation to be observed (Smith and Foster, 2008, Smith et al., 2009b).

Scholey et al. (2009a) demonstrated glucose facilitation of a secondary tracking task, but not the memory component of the task. This task required the participants to accurately track an on-screen asterisk moving unpredictably across a screen whilst word stimuli were presented auditorily. Whilst memory performance was not enhanced, Scholey et al.'s (2009a) study does indicate that glucose enables increased availability of resources during a dual task, through allowing tracking improvements without impairing memory. This may account for the findings of glucose memory enhancements during other dual task paradigms, such as the memory with hand movement task. It is possible that due to the increased monitoring (and hence cognitive processing) required to accurately switch between the hand movement sequences, the glucose load is enabling a larger processing capacity that is ameliorating deficits in either memory performance or performance on the secondary task that might otherwise occur. However, the impact of glucose on the dual

hand movement task itself is difficult to quantify due to any scoring of the hands task being highly subjective, subsequently it is rarely scored (often camcorders are set up to aid compliance but do not actually record). Scholey & Fowles (2002) reported that glucose enhanced kinaesthetic memory performance, which raises the possibility that hand movement performance has the potential to be facilitated in conjunction with memory. However, Scholey et al. (2006) did score correctly performed hand movements, finding no significant treatment effects.

Awad et al. (2002) reported a glucose amelioration of impairments on the highly demanding reconstruction task, with glucose failing to enhance performance on the less demanding free recall. However, Messier et al. (2003), failed to find a glucose enhancement on the same reconstruction task in older adults, questioning the robustness of this finding. Meikle et al. (2005) also reported a glucose facilitation effect only for more challenging stimuli (low imagery as opposed to high imagery words and longer word lists as opposed to shorter). Increasing the effortfulness of cognitive processing (through hand movement) has been shown to reduce circulating blood glucose levels in conjunction with global impairments in memory (Scholey et al., 2006). In the same study (Scholey et al., 2006), the manipulation of emotionality of words led to increased circulatory glucose, with an impairment seen in memory even though hyperglycaemia was induced by emotionality (with the dual hand movements failing to significantly reduce glucose levels in this condition). Scholey et al. (2006) did not administer a drink (glucose or otherwise), making this study difficult to directly compare with similar studies. However, the lack of dietary interventions (a 2 hour fast following a light breakfast and abstaining from alcohol the evening prior to testing), do make this study more reflective and hence informative of individuals in their normal mid morning state.

A glucose drink has also been shown to elicit enhancement effects during a period of sustained cognitive demand. Following six consecutive completions the Cognitive Demand Battery (CDB) (2 min Serial 3 subtractions, 2 min serial 7 subtractions, 5 min rapid visual information processing (RVIP) and a mental fatigue visual analogue scale), a glucose load was found to ameliorate decrements in the mental arithmetic tasks, accuracy of the RVIP task and also subjective feelings of mental fatigue during later completions (Reay et al., 2006). This further illustrates that glucose seemingly particularly enhances challenging tasks whereby performance (through increased stimuli difficulty, sustained demand or divided attention etc) is prevented from nearing ceiling levels. Again the evidence for this is not robust, with alternative research failing to find this effect. Manipulating the task difficulty during an episodic memory task (unrelated paired associates or memory for concrete [easy] or abstract [difficult] words) failed to elicit a

glucose facilitation when a secondary card sorting task was employed (Riby et al., 2004a, Riby et al., 2006). However, accuracy and reaction time measures did indicate the difficulty manipulation was successful (Riby et al., 2006), although the possibility that these particular secondary tasks were not sufficiently demanding to elicit decrements should not be ruled out.

The influence of glucose is not limited to cognitive manipulations of effortful demand, but also has wider reaching social implications. Acts of self control which are cognitively demanding processes to control and deplete circulatory glucose levels, impairing subsequent self control on controlled or executive processes (Gailliot et al., 2006). This also has implications on behaviours further reaching than memory, with poor self control a leading cause of criminal behaviour (Pratt and Cullen, 2000) and poorer glucoregulation linked to criminal behaviour (Virkkunen and Huttunen, 1982) and aggression (Donohoe and Benton, 1999a).

1.4 Potential Mechanisms Underlying the Glucose Memory Effect

There are several theories which attempt to explain the mechanism behind the glucose memory facilitation effect. Several of these all propose rational explanations, yet the specific mechanism or mechanisms behind the effect remains to be fully understood. Various suggested mechanisms propose that raising glucose levels leads to glucose acting directly on the brain by altering neural metabolism, neural activity and / or neurotransmitter synthesis (Korol and Gold, 1998). Alternative approaches suggest that it may be peripheral processes / organs that mediate the glucose effect on cognition, e.g. the liver or insulin effects (White, 1991). Additionally there is disagreement in the literature as to whether the task domain ('domain' approach) or level of demand ('demand' approach) exerted by a task is the more important determinant factor in eliciting glucose facilitation. This section will explore several of the mechanisms that have been suggested to mediate the glucose facilitation effect.

The bulk of the literature to date suggests that glucose is preferentially targeting memory, and subsequently several authors postulate that glucose is acting preferentially on the hippocampal domain of the brain, known to be key for memory and learning (Winocur and Gagnon, 1998). The postulation that the hippocampus is preferentially susceptible to glucose administration and is subsequently the key factor in glucose facilitation mediation of memory, has been referred to as the domain approach. Increased hippocampal functioning may be facilitated by several (yet to be verified) routes. Messier et al. (1990),

suggest that raised circulatory glucose levels may increase synthesis of the neurotransmitter acetylcholine. Messier et al. (1998) reported that the effect of glucose appears to be localised on the recall primacy effect, an effect also seen following administration of cholinergic drugs. This is supportive of the postulation that glucose acts on memory through an interaction with brain cholinergic systems. The metabolism of glucose forms acetyl CoA which is a precursor for acetylcholine, making this an intuitive potential mechanism.

As discussed in section 1.2.4, administering a glucose load elicits a rise in circulating blood glucose which in turn leads to a corresponding increase in circulatory insulin levels (amongst other hormones such as glucagon and somatostatin). The hormone insulin may also exert influence on the brain, as insulin receptors are present in the brain in various concentration levels and insulin does cross the blood brain barrier through active transport (Park, 2001). The hippocampus contains a high concentration of GLUT 4 receptors which are insulin sensitive. The firing rate in the hippocampus has been shown to be sensitive to insulin, as has glucose metabolism and glucose uptake in this area (Hoyer, 1996, Hoyer, 2003). It has been suggested that the rise in circulatory insulin evoked by raised glucose levels, may be the determinant either as the primary substance promoting facilitation or through promoting increased glucose utilisation at the hippocampus (Craft et al., 1994). Consequently insulin may have a direct impact on cognition, separate or linked to that of its glucoregulatory functions.

An alternate view is that rather than the glucose effect specifically targeting one area of the brain, it is a global effect evoked by raised glucose levels. Support for a global effect of glucose is gleaned from the interaction of glucose with several neurotransmitters acting throughout the brain; dopamine (Saller and Kreamer, 1991), serotonin (Fernstrom and Wurtman, 1971), acetylcholine (Messier et al., 1990) and opiates (Lux et al., 1988). Glucose has been found to counteract the pain reducing property of the opiate morphine in mice (Lux et al., 1988). The authors suggest that this is a direct effect of glucose (and fructose which also elicited this effect) or their metabolic product within the CNS. Cholinergic agonists enhance, whereas cholinergic antagonist impair memory. Opiate agents on the other hand have the reverse effects, with antagonists enhancing and agonists impairing memory (inhibitory avoidance and spontaneous alternation tests of memory, plus non memory measures such as electrographic sleep, locomotor activity and tremors), suggesting that opiates inhibit cholinergic function (Gold, 1991). When studying glucose in conjunction with these pharmacological interventions, glucose was found to exaggerate the enhancing effects of cholinergic agonists and limit the detrimental effects of cholinergic antagonists on a range of memory indices. Glucose also attenuated the

effect of opiate agonists (Lux et al., 1988). It has also been postulated that under certain conditions, circulatory glucose may limit the production of acetylcholine synthesis via the availability of the substrate Acetyl-CoA during metabolism. These interactions between glucose and opiates / cholinergic function, provide considerable evidence to the theory that glucose is mediating neuronal activity and hence memory via the production of the neurotransmitter acetylcholine. Further a glucose or adrenaline load (which leads to increased glucose levels) limits the memory deficits induced by scopolamine, which has anticholinergic properties.

Glucose facilitation has been shown to be more readily detectable in healthy adults during cognitively demanding tasks. Evidence investigating the modulation of memory by the hormone adrenaline have found that both exogenous and endogenous adrenaline enhance memory (Gold and McCarty, 1981, McCarty and Gold, 1981) in rats (endogenous levels controlled through the strength of a foot shock in rats). This enhancement was found to give an inverted-U dose response and was detectable even when the adrenaline was given immediately post task (during consolidation of memory). The facilitatory effect of adrenaline is shown to decrease in line with the increased time lapse following task completion and administration. Adrenaline is released into the blood stream as a result of stress via the sympathetic nervous system and leads to several important physiological responses; vasoconstriction increasing blood pressure and delivery of key energy nutrients (glucose and oxygen around the body), increased heart rate and increased glycolysis and subsequent circulatory glucose levels. Adrenergic antagonists however, prevent such memory enhancement occurring (Gold, 1991). This suggests that adrenergic receptors may also play a considerable role in the mechanisms which act to affect memory. This is particularly salient as adrenaline does not cross the blood brain barrier, as such it cannot act directly on the CNS and yet does mediate cognition, presumably through peripheral actions. It has been noted that the subsequent increase in glucose levels evoked following adrenaline administration and through endogenous release (e.g. in electric foot shock studies), are at a similar level (25-50 mg/dl above baseline 120 mg/dl) to those induced by a glucose load which also elicits memory enhancement in rats (Gold, 1991, Hall and Gold, 1986). Support is gleaned for the adrenaline memory facilitation being attributable to the increased glucose levels by Hall and Gold (1986) . Hall and Gold (1986) administered adrenergic antagonists to block the effects of adrenaline to rats during inhibitory avoidance training, but post task administered a glucose load. The adrenergic antagonist failed to attenuate the memory effect seen following adrenaline, indicating that the raised glucose levels were inducing the effect.

Administration of a glucose load has been found to selectively facilitate performance on cognitively demanding tasks (see section 1.3.5). This increased susceptibility suggests that cognitive loading may be the most important determinant in eliciting glucose facilitation, and has been dubbed the 'demand' approach. By increasing the activity required to successfully complete tasks, brain energy demands increase. Intuitively, the theory that increasing the availability of fuel to the brain enables increased capacity for work, and avoidance of a potential energy deficit impeding performance, is an attractive one. However, the homeostasis of glucose levels is strictly controlled, questioning whether a fuel deficit is truly induced in the brain.

Investigating the effect of insulin on cognition is a particular conundrum in the glucose literature, with no true way to dissociate the interdependent circulatory levels of glucose and glucoregulatory hormones. This means that whilst the glucose enhancement effect is discussed, the enhancements may be in part, or entirely attributable to secondary endocrine effects of glucose supplementation, rather than the glucose load itself. Clamping studies have allowed investigations attempting to dissociate the effect of glucose from other hormones, representing the most controlled manipulation of physiological responses. In euglycemic (blood glucose level is maintained at fasting concentration) and hyperglycaemic (blood glucose is elevated) clamping studies, glucose levels are continually sampled with simultaneous infusions of glucose and regulatory hormones (primarily insulin and somatostatin as discussed above in section 1.2.4) to maintain the desired physiological state. However, in order to maintain levels of either glucose or regulating hormones, at hyper or hypo concentrations, additional infusions must also be made to maintain required levels. Elevated levels of insulin for example, will continually elicit glucose storage as glycogen through glycogenesis. This causes circulatory glucose levels to fall and subsequently more glucose needs to be infused in order to maintain glucose levels. These counteracting effects may allow examination of potential effects of administering insulin, but since glucose must also be administered, any observed effects may not be solely attributable to the substance in question. In Watson and Craft's (2004) study, the memory enhancing effects of raising exogenous insulin levels using euglycemic clamping are described, however, the authors also note that since glucose is also administered, the effect cannot solely be attributed to insulin. This is an area where examining abnormal populations can help illuminate the underlying mechanisms. Abnormal populations are discussed in section 1.3.3.1.

Whilst intuitively appealing, simply increasing the availability of glucose and therefore capacity for information processing, is somewhat simplistic. The circulatory supply of glucose is tightly controlled with the availability through the blood brain barrier remaining

almost constant, with little evidence that the availability of glucose to the brain influences glycolysis (Benton, 2005). Rather the rate limiting factor in glucose metabolism within the brain appears to be the hexokinase enzyme, which is key to glycolysis (Pardridge, 1983).

1.5 Rationale, Aims and Objectives

The research considered throughout this introduction has provided evidence that glucose can facilitate cognitive functions in a range of populations; young and elderly, normal and abnormal. Memory performance has continually been shown to be susceptible to facilitation following a glucose load, with verbal declarative memory seemingly the most consistently enhanced. However, to date there is no conclusive evidence as to the mechanism (or mechanisms) by which glucose is enhancing memory. To further confuse the literature, often the reported results across studies are contradictory. This questions the assertion that the glucose effects observed are a) robust and b) equally effective across populations. One issue with regards to the published literature to date is the variety of methodologies utilised including; different doses, drink volumes and content (e.g. saccharine vs. aspartame, flavouring vs. no flavouring), testing times and schedules, pre test fasting periods and dietary controls etc. It is also conceivable that studies failing to generate significant findings are less likely to published, skewing the overall representation of the published findings.

Declarative memory seems to be the most consistently enhanced aspect of memory following a glucose load. The memory tasks utilised to date have generally relied upon standard declarative memory tasks such as word recall and recognition. Subsequently such research has built a firm foundation, allowing various comparisons to be made across several populations with unique features particularly pertaining to glucoregulatory control. Whilst facilitation of declarative memory via word recall tasks appears on the surface to be simple, there are several aspects of performance that does not allow a full interpretation of the glucose effect. These will be addressed throughout this thesis by utilising a variety of paradigms, specifically selected and designed to evaluate the impact of glucose at the various stages of memory; encoding, consolidation, and retrieval. Whilst glucose has been shown to mediate performance on a range of cognitive tasks, along with the implications of memory impairments across several populations (ageing, AD, DS and diabetes / metabolic syndrome), this thesis will concentrate on explicit declarative memory, which in itself holds immense scope for investigation. As healthy young adults have been shown to be susceptible to glucose facilitation of this performance measure (at

least in instances whereby the task is sufficiently demanding), this is the population utilised throughout this thesis (experimental chapters 3, 4, 5 and 6).

However, whilst considering declarative memory as a whole has allowed for some interesting insight, declarative memory consists of several dissociable processes. The various stages and processes involved in declarative memory may be specifically / differentially targeted by a glucose load. This thesis will concentrate primarily on evaluating the relative effect of a glucose load on different processes of declarative memory, in conjunction with individuals' levels of glucoregulatory control.

To date, several of the paradigms employed in this thesis have not been integrated into exploratory research investigating nutritional interventions on behaviour. The paradigms adapted for use in this thesis have the potential to provide a basis for the development of novel tasks and techniques, in order to further understand not only how glucose mediates memory, but may also be used to investigate other nutritional and pharmacological effects.

1.5.1 Summary of Thesis Aims and Objectives

The overall aims and objectives of this thesis are summarised below:

- Research published to date has inferred declarative memory is the most susceptible to the glucose facilitation effect. However, the standard paradigms used cannot infer specifically which aspects of declarative memory may be being targeted by / susceptible to the glucose enhancement effect. With particular reference to memory efficiency and in particular forgetting, this thesis aims to employ novel paradigms from the cognitive literature to explore this issue.

- To further the existing knowledge on the influence of an individual's level of glucoregulatory control on both declarative memory and any potential interaction with glucose facilitation. By investigating young healthy adults, who are unlikely to be affected by confounding health damage related to poorer glucoregulation (e.g. cerebrovascular damage), any glucoregulatory interaction found should be reliably attributed to the effects of glucoregulatory control.

- Through manipulating circulatory blood glucose levels and task demand (in conjunction with measures of glucoregulatory control), this thesis aims to further elucidate the mechanisms by which glucose may be enhancing memory.

- Additionally, a distinct gap in present knowledge pertaining to the influence of glucose administration is addressed. Using a wide range of tasks an overview is sought as to how various glucose doses may influence cognition in children.

1.5.2 Experimental Chapter Aims

In order to address the overall aims of this thesis (identified in the previous section), five studies in total were conducted. The title along with the primary aim of each study is given below (specific hypotheses are given in the chapters):

- Chapter 2: *'A dose response investigation of the impact of glucose on cognition in 10 year olds.'*

  Aim: To address the gap in existing literature regarding the influence of a range of glucose doses on cognition in children.

- Chapter 3: *'The effect of glucoregulatory control and glucose facilitation on recollection and familiarity components of memory during the remember/know paradigm.'*

  Aim: To further the current literature investigating the impact of glucose and glucoregulation on recollection and familiarity processes, in order to dissociate whether the glucose facilitation effect is preferentially targeting the hippocampus ('domain' approach) or a more global facilitation during highly demanding cognitive processes ('demand' approach).

- Chapter 4: *'An evaluation of the impact of glucoregulatory control and glucose facilitatory effects on encoding efficiency, via the item method directed forgetting paradigm.'*

  Aim: To investigate whether the potentially facilitating effects of glucose are preferentially targeting encoding efficiency through intentional forgetting, and whether encoding efficiency impairments may be a resultant feature of poor glucoregulatory control.

- Chapter 5: *'An investigation of glucoregulatory and glucose facilitation effects on inhibition through retrieval induced forgetting.'*

  Aim: To investigate whether any effects of glucose are preferentially targeting inhibition processes of items that are semantically related, and whether impairments in inhibition may be a resultant feature of poor glucoregulatory control.

- Chapter 6: '*An evaluation of glucoregulation and facilitation effects of glucose on the memory blocking effect.'*

  Aim: To investigate role of glucose and glucoregulation on the inhibition / blocking of orthographically similar items from recall and the effectiveness of the executive control processes required to overcome the inhibition / blocking.

CHAPTER 2. A DOSE RESPONSE INVESTIGATION OF THE IMPACT OF GLUCOSE ON COGNITION IN 10 YEAR OLDS.

2.1 Introduction

A plethora of evidence was evaluated in chapter 1 that demonstrated the beneficial properties to cognitive functioning following consumption of a glucose containing drink in adults, across a range of ages (see section 1.3.3). The facilitating effects of glucose are well accepted (Messier, 2004), with certain tasks seemingly more susceptible to facilitation than others, for example explicit declarative memory (Riby, 2004), and studies that have employed highly demanding/dual task paradigms (Kennedy and Scholey, 2000, Messier, 2004, Scholey et al., 2001, Scholey et al., 2006, Sünram-Lea et al., 2002a, see also section 1.3.5).

However, to date, very few studies have been conducted in children to ascertain the influence of glucose on cognition in this population. There is good reason to conduct a well designed and controlled study in this population, not least because evidence to date is very limited. The brain is the most metabolically demanding organ in the body, more so within the first decade of life. Cerebral blood flow (an indirect measure of energy demand) is almost twice that of young adults in 3 to 11 year olds, with oxygen utilisation 1.3 times greater in children than adults (Kennedy and Sokoloff, 1957). Position emission tomography (PET) has allowed mapping of the metabolic maturation of the infant brain. At birth metabolic rates of glucose utilisation are approximately 30% lower than that observed in healthy young adults (Chugani, 1998). Over the first 4 years of life, metabolic rates of glucose utilisation soar to 55-60 μmol/min/100g of mass, which is over twice that observed in adults. This high metabolic rate is maintained until approximately 9-10 years of age (Chugani, 1998, Kalhan and Kilic, 1999). Thereafter this rate slowly declines to adult levels by the age of 16-18 years (Chugani, 1998), to approximately 30 μmol/min/100g of mass (Kalhan and Kilic, 1999).

Such a high metabolic rate of glucose utilisation in infants, may suggest that children could potentially glean greater cognitive benefits from glucose than those observed in adults. However, the evidence to date is limited and somewhat contradictory. To date only three published studies have examined the effect of a glucose drink on healthy children's cognitive performance (Benton and Stevens, 2008, Benton et al., 1987, Wesnes et al., 2003), although there has been considerable focus placed on assessing cognitive

function following various glycaemic loads in the form of breakfast cereals and snacks. Two of the three studies examining the effects of a glucose drink have reported positive effects of glucose (Benton and Stevens, 2008, Benton et al., 1987), however, the findings are not robust, with several methodological issues and limitations within the studies, capping the scope for generalisation of findings.

The first published study examining a glucose drink in children administered a 25 g glucose drink to 6-7 year olds (Benton et al., 1987). This study employed the Shakow (1962) paradigm to assess the children's ability to sustain attention, whereby following a verbal warning and a set delay (of 3 or 13 seconds), a light appeared which demanded a button press reaction. The results showed faster reaction times following glucose rather than placebo following both 3 and 13 second delays. The authors discuss this finding in terms of a glucose load facilitating sustained attention. Frustration was also assessed through coding children's behaviour during repeated completions of an unfamiliar difficult task (an early 1980s computerised 'tennis' videogame). Children were found to spend more time on task 'quietly concentrating' throughout, having consumed the glucose treatment. During the second half of the trials, children who had consumed glucose also exhibited less fidgeting, fewer signs of frustrations and less talking, than those in the placebo group. Whilst these findings are interesting, it should be noted that this study took part in the afternoon after lunch. No dietary restrictions or controls were included, subsequently other influences may have impacted upon the results e.g. caffeine or the varying glycaemic loads of the lunches consumed.

Benton and Stevens (2008) furthered the above research in 9-10 year olds, also using a 25 g glucose drink. The Shakow paradigm (Shakow, 1962) was again utilised, however, no influence of a glucose load on sustained attention was found. Observations of classroom behaviour were made over a 20 minute period, during which the children worked as individuals completing maths problems. The data indicated that relative to placebo, glucose increased time spent on task but only over the course of the second half of observations. This indicates that whilst sustained attention on the Shakow paradigm was not improved, naturalistic environmental behaviour involving the ability to concentrate was. These findings question the robustness of glucose facilitation on this aspect of cognition in children. Memory was also assessed, with picture (but not spatial) memory improved following glucose compared to placebo. As per the 1987 study, testing was conducted in the afternoon with no dietary restrictions imposed. The conflicting results on concentration and attention following glucose warrant further exploration in order to gain insight as to its susceptibility to increased circulatory glucose.

Wesnes et al. (2003), investigated attention and memory using a wider range tasks over the course of a morning (8 am baseline until 12.30 pm visit completion) following no breakfast, low GL breakfast (28.7 g carbohydrate, including 16.0 g complex carbohydrates), high GL breakfast (38.3 g carbohydrate, including 25.2 g complex carbohydrates) or 38.3 g glucose drink. Dietary restraints were similar to those imposed in the current study, with a fasting period from 8 pm the evening before, drinking only water during this period. The children in this study ranged from 9–16 years (mean age of 12), with testing completed on consecutive days. Neither attention or episodic memory were improved following the glucose drink, with performance impairments observed on these measures to a greater extent following glucose than no treatment (over the 2 hour post dose period). At all time points glucose was found to impair performance in comparison to a low and high GL breakfast.

On the basis of the above studies, no clear pattern as to the effect of glucose on children's cognition has emerged so far. While some comparison between the studies published to date may be drawn, there are several obvious differences that may be influential in mediating the effects (or lack of) observed to date. Firstly the age of the participants; 6-7 year olds (Benton et al., 1987), 9-10 year olds (Benton and Stevens, 2008) and 9-16 year olds (Wesnes et al., 2003). As the metabolic rate of the brain changes so drastically over the first 2 decades of life, the effects of a glucose intervention is unlikely to elicit the same responses to the same magnitude in these different age groups. Secondly the doses and volumes used across the studies make comparisons difficult, Wesnes et al. (2003) used 38.3 g in 330 ml of water, as opposed to Benton et al. (1987, , 2008) who administered 25 g in 250 ml. As the response to glucose is believed to be dose dependent (inverted 'U' dose response), it is likely that the impact of the higher vs. lower doses may elicit different responses, possibly triggering different mechanisms (Messier, 2004). A further consideration is the volume of the drinks. These may exert an influence through gastric intestinal tract e.g. volume sensing and via appetitive hormones which also have the capacity to influence cognition performance e.g. ghrelin has been shown to modulate memory (Atcha et al., 2009). Time of day differences may limit the comparability of Benton's work with the morning studies conducted in both adults and children, as levels glucoregulatory control fluctuate throughout the day (Van Cauter et al., 1997). Greater increases in circulating glucose are associated with identical meals received in the afternoon as opposed to the morning, with high circulatory levels associated with poorer glucoregulatory control (Owens et al., 1996, Van Cauter et al., 1997). As Benton's studies tested in the afternoon, it may be that at this time participants were more susceptible to improvements due to the decrements in glucoregulatory control later in the day. Whilst this testing period may have allowed glucose improvements in cognition to be observed,

lack of dietary control (no standardised meal / matching of food intake prior to the test sessions) limits these results as confounding variables may be at work. Whilst enforcing a fasting period prior to testing eliminates some of these variables, the glycaemic index of the previous meal may elicit the 'secondary meal effect', altering the physiological response to subsequent glucose ingestion (Liljeberg et al., 1999, Stevenson et al., 2005, Wolever et al., 1988, Wolever, 2003).

Given the above it seems likely that the cognitive performance of children may be at least, if not more, susceptible to glucose than that of adults. However, to date no study has addressed the issue of determining the optimal dose of glucose to maximise performance. A recent meta-analysis concluded that 25 g glucose load is a more effective dose for young adults (Riby, 2004), although this comparison was with larger doses and it is possible that lower doses may be more effective in children. Equally due to increased metabolic rate, larger doses may be required to satiate increased energy demands. Dosages of 0 g, 20 g and 40 g of glucose were selected for this study. These values should allow comparisons to be made with regard to the previously published literature.

This study aimed to address the following questions:

- Is cognition in children, whose brain metabolic rate is greater (approximately double) that observed in adults, susceptible to glucose facilitation as has previously been observed in adults?

- Specifically which aspects of cognition are mediated by increased circulatory glucose availability in children?

- Should glucose facilitate performance in children, what doses are effective to elicit this enhancement? Over what period does any glucose effect occur?

2.2 Materials and Method

2.2.1 Design

Participants completed a number of tasks in order to assess cognitive effects in this placebo-controlled, double blind, randomised, 3 x 4 crossover design. The variables were treatment (placebo, 20 g glucose and 40 g glucose) and time (baseline, 30, 60 & 90 minutes post-dose).

Participants were randomly allocated to treatment orders as selected through a Williams Latin Square, such that each treatment followed each other treatment an equal number of times.

2.2.2 Participants

Thirty-six children aged 10 years (13 males, BMI Mean 18.33, *SD 2.12*) completed the study, see appendix 1.1 for individual participant characteristics. Participants were recruited through opportunity sampling from the Newcastle-upon-Tyne area. All participants were reported to be healthy, free from allergy, not using medication nor taking dietary supplements. Participants were tested following an overnight fast from 10 pm (they were instructed to drink only water during this period). Testing took place at 8.30 am and continued over 2.5 hours. Written informed consent was sought from the participants and parents / guardians. Children received shopping vouchers worth £80 addressed to them following completion of the study. Parents received a contribution of £10 towards travel expenses incurred.

2.2.3 Treatments

Test treatments were comprised of either 20 g glucose, 40 g glucose, or a saccharine placebo, made up to a volume of 150 ml with water.

Participants were administered the drink in isolation under the direct supervision of the researcher, with a maximum of 5 minutes in which to consume the drink, with the end of the drink consumption time locked as 0 mins (t=0). Study day drinks were prepared by a

disinterested third party in order to ensure the study remained double blind. Drinks were made the evening prior to the participants visit and were kept refrigerated overnight in sealed containers.

2.2.4 Assessment

Each completion of the test battery was comprised of a wide variety of tasks in order to assess a range of cognitive domains; Memory Recall (Immediate and Delayed memory), Speed of Information Processing (Number Search), Continuous Attention, Working Memory (Serial Sevens Subtractions), Verbal Fluency (Word Generation/Retrieval), Arrows Reaction Time & Flankers (focused and selective attention) and mood/satiety scales. These tasks and similar versions of them have been shown to be sensitive to dietary intervention in children of similar ages (8-14yrs) (Haskell et al., 2008, Ingwersen et al., 2007, Kennedy et al., 2009, Wesnes et al., 2003). The tasks were completed in the set order as shown in figure 2.1a, and are described in detail below.

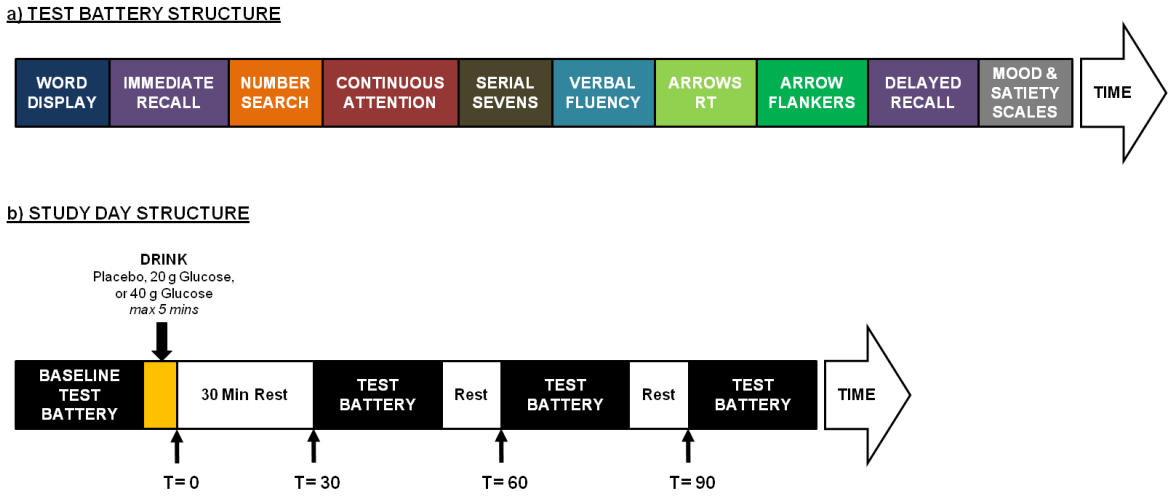


Figure 2.1 Schematics of the structure of study visits*; a) the test battery and b) study day structure.*

2.2.4.1 Word Recall

Fifteen words were presented on screen for 2 sec, with an inter stimuli interval of 1 sec. Immediately following presentation and prior to completion of the mood and satiety scales (typically 20 min later) participants were given 1 minute to write down as many words from the list as they could remember. Word were selected and lists matched on the following

parameters; number of syllables 1-3 (Mean 1.673, SD 0.664), number of letters 3-9 (5.577, *SD 1.48*), Kucera-Francis word frequency 20-100 (Mean 55.193, *SD 31.371*), imagery rating 3-7(Mean 5.853, *SD 0.892*), concreteness rating 3-7 (Mean 6.101, *SD 1.113*), meaningful rating 4-8 (Mean 6.462, *SD 0.825*).

2.2.4.2 Number Search

The number search is a test of selective attention and speed of information processing, which is similar to the Sky Search task from the Test of Everyday Attention in Children (TEA-Ch) battery (Manly et al., 2001) and the computerised rapid visual information processing task (Krupski et al., 1971). It has been successfully used with children previously (Heatherley et al., 2006) and has been shown to be sensitive to nutritional interventions e.g. caffeine. One page of numbers (2 blocks of 40 x 12 numbers, 45 targets per block, 2-5 targets per row) were presented and participants asked to circle pairs of consecutive even numbers, working from left to right and row by row as quickly and as accurately as possible. Four minutes were allowed to complete this task. Please see appendix 2 for an example of this task.

2.2.4.3 Continuous Attention

In a computerised version of the task, letters were sequentially presented on screen and participants hit a key (spacebar) in response to a target combination (e.g. 'C' immediately followed by 'T'). The letters A-Z were presented in pseudo-random order at a rate of 100 letters per minute for 3 minutes. A total of 24 targets are presented at a rate of 8 per minute. The target letter pair remained on screen throughout the task.

2.2.4.4 Serial Sevens Subtractions

The task was originally designed by Hayman (1942), and is sensitive to both lowered (Taylor and Rachman, 1987) and raised (Kennedy and Scholey, 2000, Scholey et al., 2001) blood glucose levels. This study utilised a computerised version of the serial subtraction tasks. Participants counted down from a random starting number (between 375 and 399 but not 384, 391 or 398 to prevent the participant from using existing knowledge of the 7 times tables). The starting number appeared in the centre of the

screen and disappeared following the input of the first response. Responses were entered using the linear number keys situated towards the top of the keyboard, with asterisks appearing onscreen in place of the actual digits. Once the 3 digit response had been input, pressing 'Enter' submitted and cleared the response from the screen. Participants could use the 'Backspace' key to delete errors. In the case of an error participants were instructed to continue subtracting from the last number entered, with subsequent responses are scored in relation to that response. The task length was 2 minutes and scored for the number of correct responses.

2.2.4.5 Verbal Fluency

This is a classic test of executive function (although it does contain elements of retrieval). Participants generated (wrote down) as many words as possible beginning with a given letter (for example 'F', 'A' or 'J') within 2 minutes. A total of 16 letters were required, 'Q' and 'V' to 'Z' were not used. All other letters were randomly selected and assigned to a specific visit number and time point.

2.2.4.6 Arrows RT – Focused Attention

An arrow appeared on screen pointing to the left or right. Participants responded as quickly and accurately as possible with a 'z' (left arrow) or 'm' (right arrow) key press, corresponding to the direction of the arrow. Each of the 80 stimuli remained on screen until the key press was registered. There was a randomly varying inter-stimulus interval of between 200-600 msec.

2.2.4.7 Arrow Flankers

Five symbols appeared on screen, with the centre symbol always being an arrow pointing to the left or right. The task was to press the 'z' (left arrow) or 'm' (right arrow) key corresponding to the direction of the central arrow. The flanking pairs of symbols were squares, crosses, congruent arrows (pointing in the same direction), or incongruent arrows (pointing in the opposite direction), see figure 2.2. Each of the 40 stimuli remained on screen until a key press ('z'/'m' keys only) was registered or until 1800 msec passed. A fixed rate of presentation was used, with each stimulus appearing 2000 msec after the

onset of the previous stimulus regardless of whether a response was made. Stimuli were randomly ordered, but consisted of 4 crosses (which require the participant to give no response), 12 squares, 12 congruent arrows and 12 incongruent arrows, with half of each flanker condition having the centre arrow pointing left and half right.

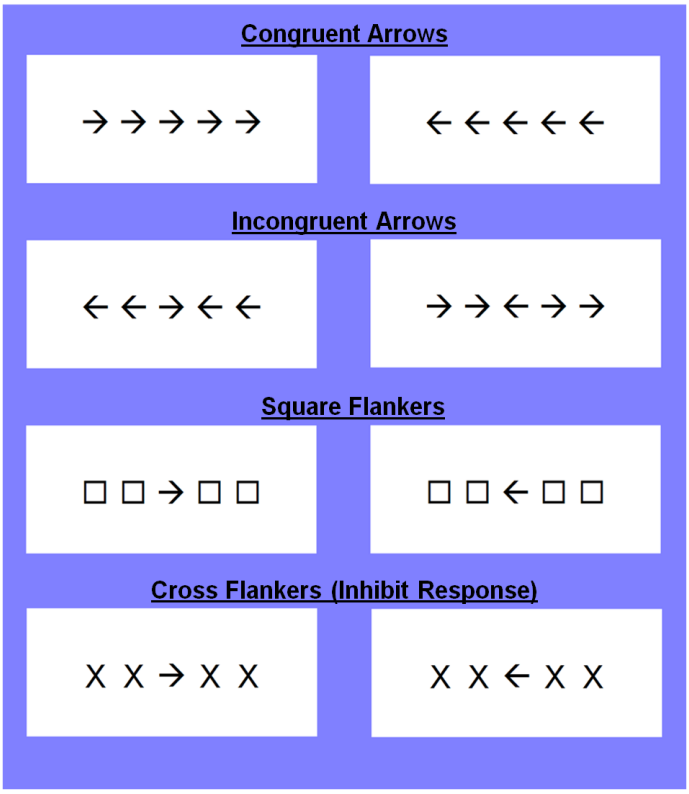


Figure 2.2 The stimuli for the arrow flankers task.

2.2.4.8 Mood & Satiety Scales

Participants indicated current mood and hunger/thirst state using computerised 100mm visual analogue scales (VAS) labelled as: 'hungry', 'full', 'thirsty', 'awake' and 'sleepy' with the end points labelled as 'not at all' and 'very'. Responses were made by clicking on the VAS in the desired position, where a cross would then appear. The location of the cross could be altered until the participants clicked to record the response.

2.2.5 Procedure

Participants visited the dedicated temperature controlled laboratory on four occasions. Participants were visually isolated whilst being tested in groups.

The training day visit comprised: obtaining informed consent; health screening; collection of demographics; random allocation to treatment order and full training via four completions of the full test battery at 30 minute intervals. Standardised instructions were read out on the first completion of the test battery, with shorter summaries given on subsequent completions.

Following the training day participants attended the laboratory at 8.30 am in a fasted state, following a washout period of at least 48 hours between visits. Participants and guardians were interviewed to check compliance with the fast and to ensure no changes to the participants' status. Food diaries (see appendix 3.1) for the 24 hours prior to each study visit were also collected and checked for compliance. Following baseline completion of all tasks, each participant consumed the treatment (9.00 am) followed by a 30 minute rest period. Participants consumed the treatments individually under supervision. Time point 0 minutes was locked to participants finishing the drink. The remaining 3 completions of the test battery were completed at 30 min, 60 min and 90 min post dose, see figure 2.1b. Each completion of the task battery took approximately 22 - 25 min to complete. During the rest periods participants sat quietly and were permitted to use the internet.

2.2.6 Statistics

Prior to the primary analysis, baseline data were subjected to a one way ANOVA to establish any baseline differences.

For each outcome change from baseline values were computed and analysed by two-way ANOVA [treatment (placebo, 20 g glucose, and 40 g glucose) X time (30, 60 & 90 min)].

Where the ANOVA revealed significant differences ($p<0.05$) post hoc pairwise comparisons were supplied with a Bonferroni correction. Only the highest order interaction effects are reported in the text. Lower order effects are indicated in the outcome tables. Whilst the main effects of time are indicated within the outcome tables, these are not presented in text since they do not address the aims of this study.

2.3 Results

2.3.1 Word Recall

A baseline difference for delayed recall errors was observed ($F(2, 33)=4.320$, $p=0.022$, $r=0.340$), however, no pairwise differences between treatments were found. No significant effects were observed for this task. See table 2.1 below for change from baseline means and SEM.

Table 2.1 Mean change from baseline scores and SEM for immediate and delayed word recall task outcomes. No significant effects or interactions were observed.

Task	Outcome	Teatment	*n*=	Post-dose change from baseline Score									Significant Effects & Interactions
				30 Min			60 Min			90 Min			
				Means	±	SEM	Means	±	SEM	Means	±	SEM	
IMMEDIATE WORD RECALL	# CORRECT	Placebo	*35*	-0.49	±	*0.29*	-0.30	±	*0.43*	-0.59	±	*0.31*	-
		20 g Glucose	*35*	-0.93	±	*0.40*	-0.66	±	*0.34*	-0.40	±	*0.25*	
		40 g Glucose	*35*	-0.73	±	*0.36*	-0.47	±	*0.31*	-0.76	±	*0.36*	
	# ERROR	Placebo	*34*	-0.21	±	*0.13*	-0.06	±	*0.20*	0.03	±	*0.11*	-
		20 g Glucose	*34*	0.03	±	*0.08*	-0.06	±	*0.13*	0.03	±	*0.13*	
		40 g Glucose	*34*	0.09	±	*0.12*	0.09	±	*0.12*	0.06	±	*0.15*	
DELAYED WORD RECALL	# CORRECT	Placebo	*35*	-1.46	±	*0.32*	-1.74	±	*0.36*	-1.09	±	*0.33*	-
		20 g Glucose	*35*	-1.90	±	*0.33*	-1.41	±	*0.32*	-1.40	±	*0.28*	
		40 g Glucose	*35*	-1.60	±	*0.33*	-1.54	±	*0.26*	-1.99	±	*0.33*	
	# ERROR	Placebo	*35*	0.46	±	*0.21*	-0.14	±	*0.21*	0.17	±	*0.22*	-
		20 g Glucose	*35*	0.63	±	*0.23*	0.09	±	*0.25*	0.09	±	*0.19*	
		40 g Glucose	*35*	0.66	±	*0.24*	0.29	±	*0.21*	0.03	±	*0.23*	

2.3.2 Number Search

No significant effects were observed for this task. See table 2.2 below for change from baseline means and SEM.

Table 2.2 Mean change from baseline scores and SEM for the number search task outcomes. No significant effects or interactions were observed.

Outcome	Teatment	*n*=	Post-dose change from baseline Score						Significant Effects & Interactions
			30 Min			60 Min			90 Min			
			Means	±	SEM	Means	±	SEM	Means	±	SEM	
# SEARCHED	Placebo	*35*	56.54	±	*14.54*	67.86	±	*17.62*	43.09	±	*20.59*	-
	20 g Glucose	*35*	66.26	±	*17.64*	69.51	±	*23.90*	52.66	±	*25.15*	
	40 g Glucose	*35*	69.91	±	*14.76*	94.69	±	*22.90*	56.69	±	*25.99*	
# HITS	Placebo	*35*	6.37	±	*2.05*	6.06	±	*2.15*	4.37	±	*2.21*	-
	20 g Glucose	*35*	6.86	±	*1.50*	6.91	±	*2.11*	5.83	±	*2.03*	
	40 g Glucose	*35*	7.77	±	*2.09*	7.94	±	*2.45*	6.29	±	*2.49*	
# MISSES	Placebo	*35*	-0.20	±	*0.61*	-0.26	±	*0.49*	-0.66	±	*0.85*	-
	20 g Glucose	*35*	0.74	±	*0.61*	0.40	±	*0.88*	-1.43	±	*0.69*	
	40 g Glucose	*35*	-0.26	±	*0.82*	0.29	±	*1.26*	-1.23	±	*1.21*	
# FALSE ALARMS	Placebo	*35*	0.09	±	*0.08*	-0.03	±	*0.29*	0.00	±	*0.43*	-
	20 g Glucose	*35*	0.26	±	*0.05*	-0.03	±	*0.05*	0.00	±	*0.08*	
	40 g Glucose	*35*	0.43	±	*0.06*	0.09	±	*0.07*	-0.06	±	*0.04*	

2.3.3 Continuous Attention

Table 2.3 shows the change from baseline means and significant effects for the outcomes for the continuous attention task. No significant treatment effects were observed for this task.

Table 2.3 Mean change from baseline scores and SEM for the continuous attention task outcomes. Significant effects are indicated in the final column *(Ti = Time, *p<0.05, **p<0.01).*

Outcome	Teatment	*n*=	Post-dose change from baseline Score						Significant Effects & Interactions
			30 Min			60 Min			90 Min			
			Means	±	SEM	Means	±	±	Means	±	SEM	
# HITS	Placebo	*31*	-1.23	±	*0.72*	-1.00	±	*0.70*	-0.94	±	*0.93*	**Ti** **
	20 g Glucose	*31*	-1.87	±	*0.70*	-1.10	±	*0.78*	-0.77	±	*0.81*	
	40 g Glucose	*31*	-2.58	±	*0.58*	-1.61	±	*0.79*	-2.42	±	*0.69*	
# FALSE ALARMS	Placebo	*31*	0.94	±	*1.18*	1.94	±	*1.36*	-2.23	±	*1.96*	**Ti** *
	20 g Glucose	*31*	1.65	±	*1.23*	1.65	±	*0.89*	-1.16	±	*1.26*	
	40 g Glucose	*31*	4.97	±	*1.80*	3.03	±	*1.83*	-0.87	±	*2.13*	
CORRECT RT	Placebo	*31*	5	±	*6*	8	±	*9*	21	±	*9*	-
	20 g Glucose	*31*	10	±	*10*	7	±	*8*	0	±	*7*	
	40 g Glucose	*31*	13	±	*9*	7	±	*9*	8	±	*11*	

2.3.4 Serial Sevens Subtractions

No significant effects were observed for serial sevens subtractions. Table 2.4 shows the change from baseline means and SEM for this outcome.

Table 2.4 Mean change from baseline scores and SEM for the serial sevens subtraction task outcomes. No significant effects were observed

Outcome	Teatment	*n*=	Post-dose change from baseline Score									Significant Effects & Interactions
			30 Min			60 Min			90 Min			
			Means	±	SEM	Means	±	SEM	Means	±	SEM	
# RESPONSES	Placebo	*34*	0.68	±	*1.06*	1.68	±	*1.08*	0.88	±	*0.97*	-
	20 g Glucose	*34*	1.03	±	*1.01*	1.62	±	*0.84*	2.06	±	*1.02*	
	40 g Glucose	*34*	2.21	±	*0.83*	2.26	±	*0.95*	1.88	±	*1.28*	
% CORRECT	Placebo	*34*	3.93	±	*5.61*	-5.96	±	*4.57*	-0.86	±	*3.71*	-
	20 g Glucose	*34*	5.55	±	*4.21*	-1.58	±	*3.38*	-0.56	±	*4.16*	
	40 g Glucose	*34*	6.21	±	*3.13*	-1.92	±	*3.46*	-5.43	±	*3.69*	

2.3.5 Verbal Fluency

Table 2.5 below shows the change from baseline means, SEM and significant effects for the verbal fluency task. No significant treatment effects were observed for this outcome.

Table 2.5 Mean change from baseline scores and SEM for the verbal fluency task outcomes. Significant effects are indicated in the final column *(Ti = Time, *****p<0.0005).*

Outcome	Teatment	*n*=	Post-dose change from baseline Score									Significant Effects & Interactions
			30 Min			60 Min			90 Min			
			Means	±	SEM	Means	±	SEM	Means	±	SEM	
SCORE	Placebo	*35*	1.19	±	*0.67*	1.61	±	*0.69*	1.89	±	*0.53*	**Ti** *****
	20 g Glucose	*35*	-2.11	±	*0.77*	-1.83	±	*0.63*	-0.66	±	*0.77*	
	40 g Glucose	*35*	-1.17	±	*0.71*	0.26	±	*0.76*	-1.13	±	*0.52*	
# RESPONSES	Placebo	*35*	1.57	±	*0.70*	1.49	±	*0.77*	1.60	±	*0.73*	**Ti** *****
	20 g Glucose	*35*	-1.66	±	*0.81*	-2.06	±	*0.73*	-0.91	±	*0.86*	
	40 g Glucose	*35*	-0.89	±	*0.80*	0.11	±	*0.85*	-0.91	±	*0.63*	

2.3.6 Arrows RT – Focused Attention

Table 2.6 below shows the change from baseline means, SEM and significant effects for the arrow RT task. No significant treatment effects were observed for this outcome.

Table 2.6 Mean change from baseline scores and SEM for the arrow RT task outcomes. Significant effects are indicated in the final column *(Ti = Time, *p<0.05).*

Outcome	Teatment	*n*=	Post-dose change from baseline Score									Significant Effects & Interactions
			30 Min			60 Min			90 Min			
			Means	±	SEM	Means	±	SEM	Means	±	SEM	
# CORRECT	Placebo	35	-1.83	±	*-0.76*	-2.26	±	*-0.87*	-1.74	±	*-1.00*	Ti *
	20 g Glucose	35	-2.06	±	*-0.81*	-2.74	±	*-1.03*	-5.20	±	*-1.23*	
	40 g Glucose	35	-1.40	±	*-1.09*	-2.09	±	*-1.08*	-2.91	±	*-0.82*	
OVERALL RT	Placebo	35	-22.37	±	*12.41*	-24.80	±	*20.27*	9.19	±	*20.40*	-
	20 g Glucose	35	10.83	±	*15.65*	-8.09	±	*20.11*	2.38	±	*18.97*	
	40 g Glucose	35	-5.07	±	*17.71*	-20.49	±	*16.99*	7.20	±	*20.81*	

2.3.7 Arrow Flankers

Table 2.7 shows the change from baseline means, SEM and significant effects for the arrow flankers task.

Table 2.7 Mean change from baseline scores and SEM for the arrow flankers task outcomes. Significant effects are indicated in the final column *(Ti = Time, Tr = Treatment, *p<0.05, **p<0.01).*

Outcome	Teatment	*n*=	Post-dose change from baseline Score									Significant Effects & Interactions
			30 Min			60 Min			90 Min			
			Means	±	SEM	Means	±	SEM	Means	±	SEM	
# CORRECT RESPONSES	Placebo	35	-0.43	±	*0.51*	-1.83	±	*0.68*	-0.80	±	*0.60*	Ti * Tr **
	20 g Glucose	35	-1.14	±	*0.44*	-3.03	±	*0.59*	-1.74	±	*0.57*	
	40 g Glucose	35	-0.94	±	*0.56*	-2.77	±	*0.66*	-1.69	±	*0.47*	
# CORRECT INCONGRUENT RESPONSES	Placebo	35	-0.23	±	*0.25*	-0.80	±	*0.28*	-0.26	±	*0.29*	-
	20 g Glucose	35	-0.14	±	*0.29*	-1.09	±	*0.23*	-0.46	±	*0.26*	
	40 g Glucose	35	-0.26	±	*0.26*	-1.09	±	*0.29*	-0.71	±	*0.25*	
OVERALL RT	Placebo	35	0.00	±	*0.02*	0.01	±	*0.02*	-0.01	±	*0.02*	-
	20 g Glucose	35	-0.02	±	*0.02*	0.02	±	*0.01*	0.03	±	*0.02*	
	40 g Glucose	35	-0.02	±	*0.02*	0.02	±	*0.02*	-0.01	±	*0.02*	

For the number of correct responses there was a main effect of treatment ($F(2,33)=4.060$, $p=0.027$, $r=0.331$), see figure 2.3. Pairwise comparison revealed fewer correct responses made following 20 g glucose than placebo ($t(33)=2.786$, $p=0.026$) and than 40 g glucose ($t(33)=2.750$, $p=0.028$).

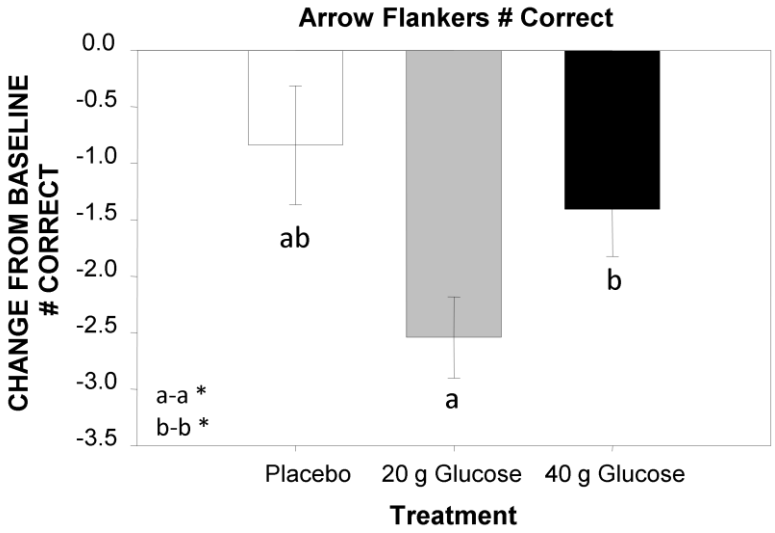


Figure 2.3 Main effect of treatment on correct arrow flankers responses *(See key on figure for significant pairwise differences).*

2.3.8 Mood & Satiety Scales

Table 2.8 shows the change from baseline means, SEM and significant effects for the mood and satiety VAS.

Table 2.8 Mean change from baseline scores and SEM for the visual analogue scales. Significant effects are indicated in the final column *(Ti = Time, Tr=Treatment, *p<0.05, **p<0.01, ***p<0.005).*

VAS Outcome	Teatment	*n*=	Post-dose change from baseline Score									Significant Effects & Interactions
			30 Min			60 Min			90 Min			
			Means	±	SEM	Means	±	SEM	Means	±	SEM	
HUNGRY	Placebo	35	2.23	±	3.73	0.80	±	2.63	-5.89	±	2.69	Ti ** Tr *
	20 g Glucose	35	9.77	±	4.08	8.03	±	3.96	2.57	±	5.67	
	40 g Glucose	35	14.49	±	2.69	5.91	±	2.55	-0.74	±	3.78	
FULL	Placebo	35	-0.63	±	3.56	-0.77	±	2.91	4.83	±	3.88	Ti ***
	20 g Glucose	35	-7.29	±	3.17	-4.66	±	2.63	1.54	±	3.40	
	40 g Glucose	35	-5.69	±	3.28	-4.57	±	3.97	-1.77	±	2.75	
THIRSTY	Placebo	35	-13.57	±	4.59	-7.71	±	3.62	-3.91	±	4.16	-
	20 g Glucose	35	-0.80	±	4.95	-1.54	±	4.77	-1.94	±	4.90	
	40 g Glucose	35	-9.51	±	4.72	1.11	±	3.23	-0.89	±	4.23	
AWAKE	Placebo	35	4.77	±	3.33	6.40	±	3.14	10.74	±	4.05	Ti *
	20 g Glucose	35	8.20	±	4.05	8.80	±	4.76	15.77	±	5.30	
	40 g Glucose	35	13.54	±	4.35	13.97	±	4.74	15.69	±	5.12	
SLEEPY	Placebo	35	-4.20	±	3.74	-2.83	±	3.43	-14.26	±	5.50	-
	20 g Glucose	35	-8.57	±	3.90	-9.77	±	4.14	-17.20	±	5.78	
	40 g Glucose	35	-9.31	±	3.70	-11.00	±	4.61	-20.09	±	4.25	

For levels of hunger there was a main effect of treatment (F(2,33)=4.944, p=0.013, r=0.361), see figure 2.4. Pairwise comparisons revealed hunger was greater following placebo than 40 g glucose (t(33)=3.094, p=0.012).

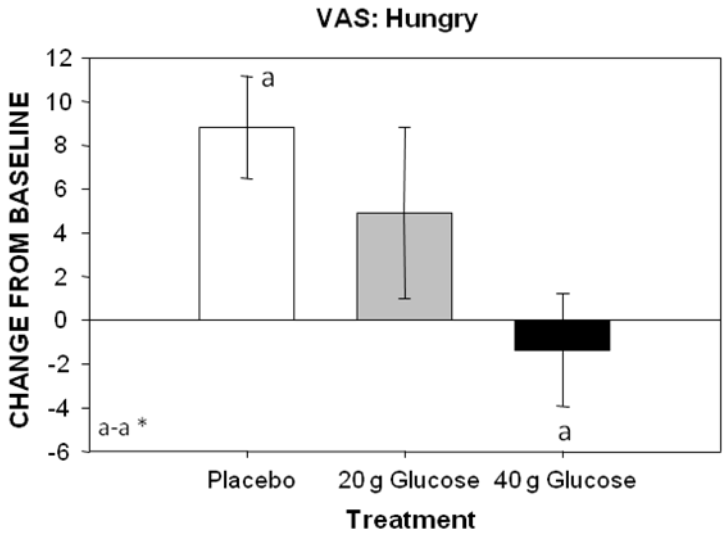


Figure 2.4 Main effect of treatment on hunger *(See keys on figures for significant pairwise differences)*.

2.4 Discussion

2.4.1 Summary of Main Findings

This aim of the present study was to address the gap in the existing literature, regarding the influence of glucose administration on cognition in children. It was postulated that due to the increased brain metabolic rate children may be as susceptible, if not more so, to any facilitating effect of glucose. In order to address this aim, a range of glucose doses (0 g, 20 g and 40 g) and tasks were employed, so as to assess which (if any) aspects of cognition are susceptible to a facilitating effect of glucose in this population.

There was very limited support for the postulation that glucose influences cognitive performance in children, with only one task revealing an effect of treatment. The number of correct responses during the arrow flankers task revealed a performance impairment following the 20 g glucose drink, with no such impairment following the placebo or 40 g glucose treatment. Of the mood and satiety measures taken, only self reported 'hunger' revealed a treatment effect. Self reported levels of 'hunger' accurately reflected the dose of glucose consumed, with an increase in reported 'hunger' levels following the placebo, and decreased levels following consumption of a 40 g load. Significant time effects were found across several tasks, which indicated that the tasks were age appropriate, with performance not reaching ceiling or floor levels. This confirms that there was an opportunity for the drinks administered to benefit or impair performance. No time by treatment interactions were observed for any outcome.

2.4.2 Task Outcomes

2.4.2.1 Memory Word Recall & Verbal Fluency

Word recall (both immediate and delayed) was not shown to be significantly influenced by any of the treatments consumed, indicating no facilitation or impairment of verbal declarative memory in this sample. This finding is contradictory to previous research which has found a 25 g glucose drink to improve immediate and delayed memory relative to a placebo (Benton and Stevens, 2008). There are several possible explanations for these different findings. Firstly, the stimuli in Benton and Steven's study were pictures on

a single card shown simultaneously, presented and recalled a total of 3 times, with recall scores accumulated. The stimuli used here were word items presented serially once. With such qualitative differences between both the stimuli and the designs employed, it is difficult to draw meaningful comparisons between these studies. However, Wesnes et al. (2003) used a very similar methodology to that employed in this chapter to assess word recall. Wesnes et al. (2003) reported a strong impairment (27%) in recall ability following consumption of 38.3g of glucose, an effect that was not replicated with the comparable 40 g dose administered here.

No treatment effects were evident on verbal fluency performance, although there was a significant time effect, which indicates there was scope available for a treatment effect on performance.

2.4.2.2 Number Search & Continuous Attention

While no effects were observed for the pencil-and-paper number search task which assesses selective attention and speed of information processing, several time effects were observed for the computerised continuous attention task. These time effects, while not particularly relevant to addressing the aims of this study, do suggest that for the continuous attention task performance participant's performance was not operating at ceiling or floor levels. This implies that the lack of any treatment effect was a true nil finding, as opposed to being attributable to task insensitivity. Previously attention has been found to be improved by a 25 g glucose drink when assessed as time spent 'on task' (Benton and Stevens, 2008) and via the Shakow paradigm (Benton et al., 1987, Benton and Stevens, 2008). This finding was not replicated here using the number search and continuous attention tasks. These findings also failed to find support for the initial attention impairment following a 38.3 g glucose drink as reported by Wesnes et al. (2003) using a similar digit vigilance task. It may be that small differences in the task parameters account for these conflicting findings. For example the CDR (Cognitive Drug Research Ltd) vigilance task used by Wesnes et al. (2003) is less demanding than the version used in this chapter, requiring the detection of single digits as opposed to a sequence of two letters.

2.4.2.3 Arrow RT and Arrow Flankers

No treatment effects were observed on the arrow RT task in which a simple left / right response was given upon stimuli presentation. The only task which did display treatment effects on performance was the more challenging arrow flankers task, in which identification of the direction of the centre arrow is made in presence of distracting (to varying levels) flanking stimuli. Relative to placebo, both 20 g and 40 g of glucose reduced correct responses, with a greater impairment observed following 20 g than 40 g. Seemingly glucose is impairing accuracy during the arrow flankers task in a dose dependent manor, with greater impairments following a 20 g than 40 g glucose load in comparison to placebo. These findings are particularly surprising, as glucose is found to be more effective in inducing performance facilitation in adults during demanding tasks (Foster et al., 1998, Kennedy and Scholey, 2000, Scholey et al., 2001, Sünram-Lea et al., 2002a), yet the opposite appears to be the case in this specific example in children. Even more surprising is the pattern of impairments induced by the different glucose loads. One potential factor that may be mediating this unexpected pattern of dose related impairments could be the influence of the hypertonic nature of the drink leading to a dehydrating effect. Hydration and thirst status have been shown to influence subsequent cognitive performance (Neave et al., 2001, Rogers et al., 2001, Scholey et al., 2009b). This introduces the possibility that the impairments observed following 20 g were the result of dehydration. Such dehydration induced deficits may have been somewhat overcome by the additional energy provision following 40 g in spite of the greater hyper tonicity of the drink (see section 7.6.2.1 for further discussion). However, self reported measures of 'thirst' were taken and no treatment effects were evident, undermining this potential cause. The possibility of hydration status change induced by the treatments cannot be ruled out though, as any hydration effects may have been subtle, with the 'thirst' VAS not sensitive enough to detect the effect.

2.4.2.4 Serial Sevens Subtractions

The serial sevens subtraction task is another demanding task, which has been shown to be susceptible to glucose facilitation (e.g. Kennedy and Scholey, 2000), and has been shown to reduce circulating blood glucose in adults (Scholey et al., 2001), see section 1.3.5 for further details. Subsequently it was expected that this task would be particularly sensitive to increased circulating glucose levels in children. However, no significant effects of time or treatment were observed for any of the outcomes from this task. As there were no time effects on serial sevens subtractions performance it is possible that for

this outcome, the task was too challenging with a resultant floor effect on performance. Alternatively the difficulty of the task may have been sufficient to prevent the children from fully engaging with task.

2.4.2.5 Mood and Satiety Scales

The only mood and satiety measure to display a treatment effect was the self reported levels of hunger. A main effect of treatment indicated that the calorific content of the consumed treatment was accurately sensed through the gastrointestinal tract, with a significant increase in reported hunger following placebo and decrease following a 40 g glucose load. Hunger following 20 g glucose was reported to increase from baseline, however, to a lesser extent than observed following placebo. The drinks administered (all the same 150 ml volume) did not influence reported levels of thirst, although undetected effects on hydration (or dehydration through the hyper tonicity of the drinks) may have gone undetected (see section 2.4.2.3 for consideration of the potential impairments induced by dehydration during the arrow flankers task).

2.4.3 Limitations

There are several aspects of the methodology used within this chapter which may impose limitation on the findings. Firstly the drinks themselves may have interrupted performance. The hypertonic nature of the drinks may disrupt cellular osmolarity, potentially disrupting performance (Brouns and Kovacs, 1997). The viscosity of the drinks and subsequent speed of gastric emptying may also have impacted on performance. Whilst possible, these findings do not fully account for the dose responses found here. The 20 g glucose drink was found to elicit greater performance impairments than a 40 g glucose drink, although it was less hypertonic and viscose. Including a no drink and / or water condition would have enabled these potential effects to be investigated. Increasing the volume of the drinks administered would decrease the viscosity and hypertonic nature of the beverages, also making the results more comparable with previous literature (38.3 g glucose in 330 ml (Wesnes et al., 2003) and 25 g glucose in 250 ml (Benton et al., 1987, Benton and Stevens, 2008).

Whilst this study was randomised and counterbalanced, there remains the possibility that treatment order effects may have influenced the data. Previous studies comparing a

glucose load to placebo have reported contradictory evidence with regards to treatment order effects. In healthy young adults, memory advantages were observed for participants receiving a glucose drink on a subsequent visit to placebo, with better glucoregulators seemingly displaying this effect to a great extent than poorer glucoregulators (Smith and Foster, 2008). In a study of children aged 9-10 years, no treatment order effects were reported following comparison of a glucose and placebo drink (Benton and Stevens, 2008). Both of these studies employed simpler designs than that utilised in this chapter, comprising of only 2 treatments and 2 treatment orders, making analysis of potential order effects more straightforward to interpret. This chapter administered 3 treatments, with 6 different treatment orders completed. Exploratory analysis of order effects was conducted (using a 3 way Treatment x Time x Treatment Order ANOVA). No interpretable order effects were observed and as such are not reported within this thesis.

As this was a study on children it was deemed inappropriate to take fingerprick blood glucose measurements. However, by doing so greater insight into the children's physiological response to the glucose loads could be achieved. Such data may have helped to disentangle some of the more difficult findings within this chapter. Blood glucose measurements would also serve as a confirmation of compliance with the fasting instructions. Although compliance was checked verbally with parents prior to each test session, a physiological confirmation would remove any ambiguity. Advances in the accuracy and reliability of non-invasive (and continuous) measurement techniques (e.g. optical techniques), may make this a practical (and ethical) option for future studies. The intense testing sessions along with short breaks which were employed here to induce a demanding environment in which treatment effects may become apparent, may be seen as a further limitation. It may be the case that the test sessions were too intense and resulted in decreased motivation and hence decreased engagement with the tasks. Wesnes et al. (2003) employed a similar length test battery with 35 minute rest periods, finding some (limited) glucose improvements (the speed items were retrieved from working and secondary memory). By incorporating longer breaks and spreading the test visit over a longer morning, any treatment effects that may have been obscured by de-motivation or mental fatigue may become apparent.

2.4.4 Conclusion

This study did not find the predicted dose dependent glucose facilitation on any outcomes across a wide range battery of cognitive tasks. Where treatment effects were in evidence,

these demonstrated impaired performance, with worse performance observed following the lower 20 g glucose as opposed to 40 g glucose, primarily on tasks requiring attention and executive control. These findings confirm that the studies investigating adult populations cannot be generalised to children of this age range. It was hypothesised that as the metabolic rate of glucose utilisation in the brains of 10 year old is approximately twice that of a young adult, children would be as susceptible if not more so, to raised circulating glucose levels. Whilst some limitations do suggest that the drinks administered in this study may have contributed to impairments / non-effects, the results here further confuse the already limited and contradictory findings to date. In these healthy children, glucoregulation is likely to be operating at a highly efficient level, which is unlikely to leave the brain undersupplied with glucose. This would make healthy children less susceptible to any facilitating effects of increased circulating glucose levels, and may explain why in adults (particularly older adults), facilitation of cognition is observed. The impairments observed here were surprising, and may hint at other dose dependent endocrine responses to the glucose impacting on performance, or alternatively resources being utilised in processing the glucose load rather than for cognition. Further work is required to establish robust replicable findings and to assess the mechanisms which may drive the impaired performance observed here in response to glucose.

CHAPTER 3. THE EFFECT OF GLUCOREGULATORY CONTROL AND GLUCOSE FACILITATION ON RECOLLECTION AND FAMILIARITY COMPONENTS OF MEMORY DURING THE REMEMBER/KNOW PARADIGM.

3.1 Introduction

The facilitating effect of glucose on memory has been well established, however, the specific neurocognitive mechanisms mediating glucose facilitation of memory have not (for reviews see; (Benton, 2001, Gold, 1991, Lieberman, 2003, Messier, 2004, Riby, 2004, White, 1991). Verbal declarative memory has been the most consistently reported aspect of memory to be facilitated by administration of a glucose load (Riby, 2004). Specifically, verbal declarative memory tasks requiring intentional recollection of previous events e.g. explicit word recall tasks (Foster et al., 1998, Messier, 2004, Scholey et al., 2009a, Sünram-Lea et al., 2002a, Sünram-Lea et al., 2008, Sünram-Lea et al., 2001, Sünram-Lea et al., 2002b). However, there is a considerable body of research which has not found this effect (e.g. Brandt et al., 2006, Ford et al., 2002a, Green et al., 2001, Kennedy and Scholey, 2000, Scholey et al., 2001, Sünram-Lea et al., 2002a).

At present there are 2 competing theories as to how glucose may enhance memory; task domain vs. task demand. The demand approach suggests that glucose preferentially facilitates performance on tasks which impose high levels of cognitive demand (Fairclough and Houston, 2004, Kennedy and Scholey, 2000, Korol and Gold, 1998, Meikle et al., 2004, Riby, 2004, Scholey et al., 2001, Scholey et al., 2006, Sünram-Lea et al., 2002a). The domain specific approach has centred around the hippocampal region and its primary role in explicit (spontaneous) recall, rather than recognition (Aggleton and Brown, 1999). As explicit recall may be preferentially targeted by glucose facilitation, the domain approach postulates that it is the hippocampal region that is targeted through raised glucose levels and hence mediates memory facilitation (Please see section 1.4 for a more in depth discussion of the relative merits of these approaches).

Further, glucoregulatory efficiency has also been shown to predict episodic memory performance (Riby et al., 2004b). Older adults appear to be particularly responsive to glucose facilitation, with declining glucoregulation in ageing being predictive of episodic memory (Riby et al., 2004b). In older adults with poorer glucoregulation, glucose was found to attenuate decrements in performance (Messier et al., 2003). However, in younger and middle aged adults, greater glucose facilitation was seen in better

glucoregulators (Meikle et al., 2004), which somewhat muddles the issue (see section 1.3.4 for further consideration of discussion).

In an attempt to explore these theories, this chapter investigates the effect of glucose and glucoregulation on 'recollection' and 'familiarity' recognition, utilising the 'remember / know' paradigm. Recognition is believed to be underpinned by two separate neurocognitive processes for 'familiarity' and 'recollection', forming two independent forms of memory (Gardiner, 1988, Gardiner et al., 1998, Jacoby, 1991, Mandler, 1980). According to Tulving (1985), 'remembering' refers to recognition in which the item/event is recollected in conjunction with contextual details e.g. the experience of seeing/being exposed to the item/event is consciously recollected. Recollection refers to the explicit recall of an event incorporating complex contextual information about the event, e.g. thoughts / feelings / images brought to mind at the time of initial exposure. As such a 'remember' response in the paradigm used in this chapter refers to recollection recognition. Alternatively 'knowing' refers to familiarity recognition whereby the exposing event cannot be consciously recollected but a feeling of 'knowing' is elicited, such that it is 'just known' that item has been previously exposed. Familiarity lacks contextual information, leaving a feeling of knowing in the absence of explicit recall (Yonelinas and Levy, 2002).

It should be noted here that while a body of research does support the dual processes approach of two distinct retrieval processes, there are alternative models advocating a single-process approaches (Vann et al., 2009). Single-process approaches postulate that 'remembering' a target during cued recall (i.e. a recognition task), merely reflects greater activation (following greater encoding at initial display), than for the weaker feelings of 'knowing' (Donaldson et al., 1996, Squire et al., 2007, Wixted, 2007). The single process account is somewhat undermined by the sparing of familiarity recognition in patient populations with disrupted recall and recollection recognition. It is these populations of individuals presenting with damage to the hippocampal area that have provided the evidence for neuroanatomical distinctions for recollection/familiarity recognition. Populations with amnesia following hippocampal damage present with impaired recall and recollection recognition, though familiarity recognition processes are on the whole spared (Aggleton et al., 2005, Holdstock et al., 2002). Aggleton and Brown (1999) suggest that connections between the hippocampus and anterior thalamus via the fornix support recollection, with connections between the perirhinal cortex and the medial dorsal thalamus supporting familiarity processes. Unfortunately, as such evidence for the dual processes approach from hippocampal damage in humans generally relies on small patient samples and case studies, there is inevitable variability in the specific locality of

damage. Vann et al. (2009) addressed this with a larger more reliable sample. Removal of colloid cysts is associated with varying degrees of damage to the mammillary bodies, which form part of the hypothalamus at the anterior arches of the fornix, relaying to the hippocampus (Vann and Aggleton, 2004, Vann et al., 2009). For these patients, detailed neurological assessments and imaging data allowed volume loss of the mammillary bodies to be accurately assessed. Patients were grouped as having sustained greater or smaller volume loss. Those suffering greater volume loss, demonstrated impaired recollection but retained familiarity recognition, with smaller volume loss also showing intact familiarity but also fewer decrements in recollection recognition. These findings add considerable weight to the dual processing approach with familiarity recognition being preserved, when damage in the hippocampal area reduces recall and recollection recognition. This chapter makes predictions based upon the dual processes approach, although the implications of the findings using the single-process approach are covered in the chapter discussion.

Several variations exist in the methodology used to assess recollection and familiarity processes (Skinner and Femandes, 2007). This chapter used the 'remember-know' procedure (Gardiner and Java, 1993), as previously employed in a glucose investigation on recollection and familiarity components of recognition (Sünram-Lea et al., 2008). The paradigm is detailed in the methodology (section 3.2). Briefly, participants complete a recognition task comprised of previously displayed (old) items and unstudied (new/novel) items, making a decision for each item as to whether the item was previously displayed. Following a recognition ('yes') response, participants are asked to make a further judgement as to whether the item is 'remembered', 'known' or 'guessed'. Using this procedure familiarity 'knowing' based recognitions are distinguished from recollection 'remember' based processes through subjective measures of 'remembering' (R) and 'knowing' (K) during recognition testing, following an initial recognition response being made (Skinner and Femandes, 2007, Vann et al., 2009). The 'guess' option prevents over inflation of familiarity 'know' responses should a guess response have been made, or that a remember / know judgement cannot be distinguished for that item.

Normal ageing has been found to lead to deficits in recollection recognition, but familiarity recognition remains relatively unaffected (Light et al., 2000, Park et al., 2010, Prull et al., 2006, Yonelinas, 2002). As poor glucoregulatory control is a feature of ageing (Awad et al., 2004), the effects of decrements in glucoregulatory controls in younger adults on recognition performance, may mirror those seen in ageing. Whilst Sünram-Lea et al. (2008), did evaluate glucoregulation indices on memory performance during this task, no significant effects were found. Due to the between participants design, treatment effects

and any interactions with glucoregulatory levels could not be assessed systematically. Studies that have investigated the neural mechanisms underlying recollection deficits in the ageing indicate that recollection deficits are related to deteriorating frontal/executive function or to medial temporal lobe function (e.g. Daselaar et al., 2006, Davidson and Glisky, 2002, Yonelinas and Parks, 2007). Should poorer levels of glucoregulation be associated with decreased recollection recognition, this may indicate that it is decrements in glucoregulatory control that are (in part) responsible for this effect in the ageing. This chapter employs a repeated measures design in order to explore this possibility.

With few studies having investigated the impact of glucoregulation and / or glucose in conjunction with this paradigm, the findings to date are far from conclusive (Smith et al., 2009b, Sünram-Lea et al., 2008).

Sünram-Lea et al. (2008) using the remember / know procedure also used in this chapter, found administration of a glucose treatment significantly increased the recollection but not familiarity component of recognition, in healthy young adults. This was interpreted as glucose administration facilitating recognition memory that is accompanied by recollection of contextual details, and as preferentially targeting the hippocampal region. The authors make the case that it is the hippocampal domain that is susceptible to glucose enhancement of recognition processes (Sünram-Lea et al., 2008). However, several limitations may serve to undermine the findings presented. As a between participants design was employed, the impact of inter participant variability cannot be ignored, recollection may simply have been greater in participants receiving glucose. Subsequently a repeated measures design was employed in this chapter, to control for any such variability. A review of the recollection and familiarity research indicates that the prefrontal cortex plays a key role in recollection (Yonelinas, 2002). Hence glucose may have been targeting the hippocampal and / or the prefrontal cortex to elicit performance enhancements in recollection recognition.

Smith et al. (2009b) investigated glucose modulation of event-related components of recollection and familiarity in adolescents. A plurality recognition paradigm was employed in which recollection and familiarity can be dissociated using event related potentials (ERPs) (Curran, 2000, Hintzman and Curran, 1994). In this paradigm 40 items were displayed during the study phase and 60 during the recognition task; 20 ‘old’ items, 20 ‘novel’ items and 20 ‘similar’ items. The similar items are comprised of words opposite in plurality from those displayed during the study phase. Upon presentation of the items during the recognition phase, only ‘yes’ or ‘no’ responses are required as opposed to Sünram-Lea et al. (2008) and this chapter, which required a further ‘remember’ / ‘know’ /

'guess' decision to be made. Determination of recollection or familiarity is made through analysis of the ERPs. The left parietal scalp sites during 400-800 ms after stimulus onset is known to reflect recollection (LP ERP component) (Rugg and Curran, 2007, Smith et al., 2009b). The FN400 component is located over the mid-frontal region, 300-500 ms after stimulus onset and has been found to reflect familiarity processes (Rugg and Curran, 2007, Smith et al., 2009b). Differences in ERPs at these sites within the stated time frames allows deduction of which processes are evoked during the recognition of 'old', 'new' and 'similar' items. This study supports Sünram-Lea et al's findings, as glucose enhancement of recollection recognition was observed. However, familiarity recognition was also enhanced, conflicting with Sünram-Lea et al.'s findings. Whilst Smith et al.'s (2009b) and Sünram-Lea et al.'s (2008) studies are not directly comparable, Smith et al.'s findings seemingly refute glucose preferentially targeting the hippocampal region and suggest more global facilitation. The use of different paradigms may account for the differences in results seen. The ERP components cannot be directly compared to the individual judgements made in Sünram-Lea et al.'s work. As Smith et al. (2009b) utilised a counterbalanced repeated measures design, between subject variability should not have biased the results, a factor which may have influenced Sünram-Lea et al.'s work. The populations tested in Smith et al.'s (2009b) study were adolescents (13 – 18 yrs) whereas Sünram-Lea et al. (2008) investigated young adults (18 – 25 yrs). As basal brain metabolic rate is higher along with better glucoregulation in younger populations, the glucose load may have been more effective in the adolescent population, with a smaller (potentially undetected) effects in the young adults.

Divided attention during the study phase of the remember/know paradigm has been found to reduce recollection and familiarity recognition performance, with a smaller (or no) effect seen for familiarity than recollection recognition (Gardiner and Parkin, 1990, Mangels et al., 2001, Parkin et al., 1995, Yonelinas, 2001, Yonelinas, 2002). Glucose facilitation of memory has been shown to preferentially target highly demanding tasks (Messier, 2004), with several experiments including secondary tasks to increase effort and / or divide attention (Smith and Foster, 2008, Sünram-Lea et al., 2002a, Sünram-Lea et al., 2008, Sünram-Lea et al., 2001, Sünram-Lea et al., 2002b). Often glucose facilitation is only apparent under these high effort divided attention constraints (see chapter 1 for a full account). As divided attention elicits decrements in recognition during the remember/know paradigm in conjunction with glucose facilitating memory performance under these constraints, this chapter includes a high effort dual demand manipulation. This manipulation will further Sünram-Lea et al.'s work and provide a greater opportunity for any potential (if small) glucose effects to be observed, further illustrating whether any

glucose effect specifically targets recollection in isolation or additionally familiarity through a more global facilitation during increased demand.

This chapter aimed to further the current literature investigating the impact of glucose and glucoregulation on recollection and familiarity processes, in order to dissociate whether the glucose facilitation effect is preferentially targeting the hippocampal domain (domain approach) or a more global facilitation during highly demanding cognitive processes (demand approach). Several hypotheses were tested:

- Should raised circulating glucose levels preferentially target the hippocampal domain, facilitation of recollection recognition processes would be observed with no effects observed on familiarity recognition.

- Alternatively should glucose elicit a more global facilitation in the brain, recognition performance for both recollection and familiarity recognition would be observed.

- As facilitation via glucose has been found to be more prevalent in tasks with greater cognitive demand, should glucose improve recognition only during the high effort manipulation, this would support the demand theory approach to glucose facilitation in memory.

- The impact of an individual's glucoregulatory control, with potential interaction with treatment on recollection and familiarity processes will be investigated. It is suggested that those with poorer glucoregulatory control will show similar performance patterns to those in the ageing, with decrements in recollection recognition but intact familiarity recognition. Poorer regulators may be more susceptible to a glucose facilitation effect on recognition processes than better glucoregulators. Increased recollection recognition in poorer glucoregulators, would provide evidence that glucoregulatory processes may be responsible for the deficits seen in ageing.

3.2 Materials and Method

3.2.1 Design

A placebo-controlled, double blind, randomised design was used. The variables were Treatment (25 g glucose or placebo) and Effort (high demand dual task or low demand non-dual task). Glucoregulation was assessed using a median split of the incremental area under the curve (AUC) for blood glucose response over the glucose low effort visit. This AUC equation for calculating glucoregulation has previously been used in similar studies (Awad et al., 2002, Smith and Foster, 2008, Sünram-Lea et al., 2008) and is given below:

AUC = [(((Pre BG – Base BG) / 2) x (15–0)) + ((((Pre BG – Base BG) + (Post BG – Base BG)) / 2) x (40–15))]

BG – Blood Glucose, Base = Baseline, Pre = Pre-Test & Post = Post-Test.

The median split was used to allocate participants to better (smaller AUC) or poorer (larger AUC) glucoregulation groups. Participants were randomly allocated to one of 24 possible treatment/effort combinations upon enrolling into the study.

3.2.2 Participants

Twenty self reported healthy volunteers (11 males, mean age 25.00 yrs, *SD 2.83*) took part in this study which was approved by the Northumbria University Division of Psychology Ethics Committee. Following completion of the study participants received an honorarium of £80. Prior to participation informed consent and screening were completed, ensuring all participants were in good health, free from illicit and recreational drugs including prescription and 'over-the-counter' medications (excluding contraceptives), did not suffer from any metabolic disorders such as glucose intolerance or diabetes, or any allergies that would prevent consumption of the treatments. All participants were non smokers. Demographic and morphometric information was recorded (BMI mean 23.51, *SD 3.45*, WHR 0.85, *SD 0.08*), see appendix 1.2 for full individual participant characteristics. Prior to each lab visit, participants fasted overnight for a minimum of 12 hours, drinking only water over this period. Food diaries (see appendix 3.2) were kept for the 24 hours prior to both visits to aid fasting compliance.

3.2.3 Blood Glucose Levels

Blood glucose levels were monitored using a Reflotron Plus diagnostic machine and Glucose Reflotron test sticks (Roche Diagnostics, Germany). The reliability of the test has previously been confirmed (Price and Koller, 1988). Blood glucose levels were measured via capillary finger prick at baseline, pre-test (15 min post dose) and at post test (~45 min post dose) for test visits.

3.2.4 Treatments

Test treatments were comprised of 25 g glucose (active) or saccharine (placebo), with 20 ml Robinsons no added sugar orange cordial, made up to a volume of 200 ml with water. The two treatments have previously been shown to present an indistinguishable taste and 'mouth feel' (Ford et al., 2002a, Kennedy and Scholey, 2000, Scholey and Fowles, 2002, Scholey et al., 2001). Evidence from the literature suggests that 25 g of glucose is an effective dose to elicit a facilitation effect on performance in healthy young adults (Foster et al., 1998, Kennedy and Scholey, 2000, Messier, 2004, see chapter 1 for an indepth consideration of doses).

Participants were permitted up to 5 minutes in which to consume the drink. Study day treatments were prepared by a disinterested third party in order to ensure the study remained double blind. Drinks were made the evening prior to the participants visit and were kept refrigerated overnight in sealed containers.

3.2.5 Assessment

3.2.5.1 Word Display

Three hundred and twenty words were selected from the Toronto Word Pool (Friendly et al., 1982). The items selected were all high frequency 2 syllable nouns, with Americanised and emotional items not selected. The words were randomised for each participant into 4 lists of 80 words. Of the 80 words, 40 were designated as 'old' and were displayed during the initial word display. The remaining 40 were 'novel', and were displayed only in the recognition portion of the visit.

The 40 ‘old’ items were presented on the centre of a screen for 2 seconds, with an inter-stimulus delay of 1 second. All letters were in lower case, see figure 3.1a.

3.2.5.2 Word Recognition with Remember / Know / Guess Determinant

Recollection and familiarity processes were assessed using the ‘remember-know’ procedure (Gardiner and Java, 1993). Eighty words were presented serially in a randomised order, consisting of the 40 ‘old’ words, and 40 additional novel items. Words were displayed in the centre of the screen, above which appeared the question ’Do you recognise this word as one that was shown earlier?’. Each word remained onscreen until a response was given by the participant. Participants were required to respond as quickly and accurately as possible via a ‘M’ key press for a positive recognition, or a ‘Z’ key press for a non recognition, by the appropriate index finger, see figure 3.1b.

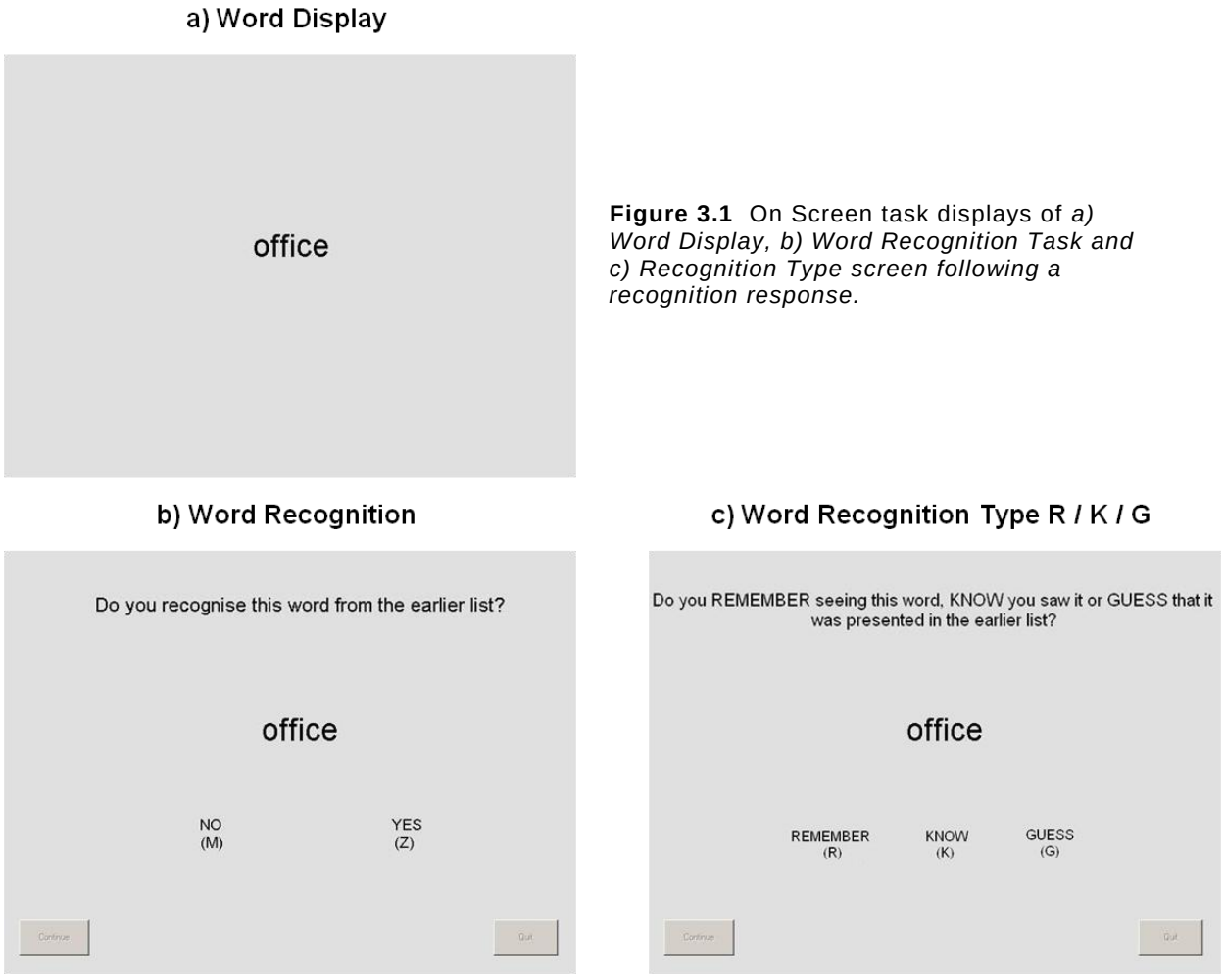


Figure 3.1 On Screen task displays of *a) Word Display, b) Word Recognition Task and c) Recognition Type screen following a recognition response.*

If a positive recognition was made, participants were then asked to categorise how they recognised the word; remember, know or guess. The distinction was made using the right index finger to press 'J' for a remember recognition, 'K' for a know (familiarity) recognition or 'L' for a guess recognition. These keys were labelled with R K G respectively to avoid confusion, see figure 3.1c. Participants were instructed to make 'remember' responses for items that they could consciously recollect as being shown during the initial word display. Such a recollection would also involve the recollection of contextual information from the initial display, e.g. thoughts or images the word evoked. Participants were instructed to give a 'know' response, to items that seemed familiar but to which they could not explicitly recall the actual display of the item. Finally 'guess' responses were to be given in the event that a participant was unsure as to whether the recognised item had been displayed previously or not.

3.2.5.3 Dual Task

A dual task was used to incite a performance deficit in individuals who otherwise may be performing at ceiling levels. This creates an opportunity for any facilitation by glucose or glucoregulatory effects to become apparent. The words are displayed visually, and so it is necessary to use a non-visual dual task, as the visual modality is engaged solely in the word display element in line with previous research utilising this paradigm. As such a continuous hand movement task which has previously successfully been employed (Foster et al., 1998, Sünram-Lea et al., 2001) was enlisted here. Participants completed complex hand movement sequences, whilst simultaneously attending to the on screen word display. Two sequences of movements were completed; sequence 1: Fist – Chop – Slap and sequence 2: Back Slap – Chop – Fist. One sequence of hand movements was completed for each word displayed. Four repetitions of each sequence were made before switching to the alternate sequence on every fifth word presentation. This switching between sequences ensures hand movements are monitored and do not become autonomous. See figure 3.2 for a photographic illustration of the dual task.

Participants were advised to complete both tasks to the best of their abilities, with no advice given to prioritise one task over the other. To ensure compliance with the hand movement task, video cameras recorded movements throughout the task and these were checked. This element of the task was briefly rehearsed during the practice visit, with written reminder sheets being issued to participants during the dose absorption period on occasions when they were required to complete the dual task.

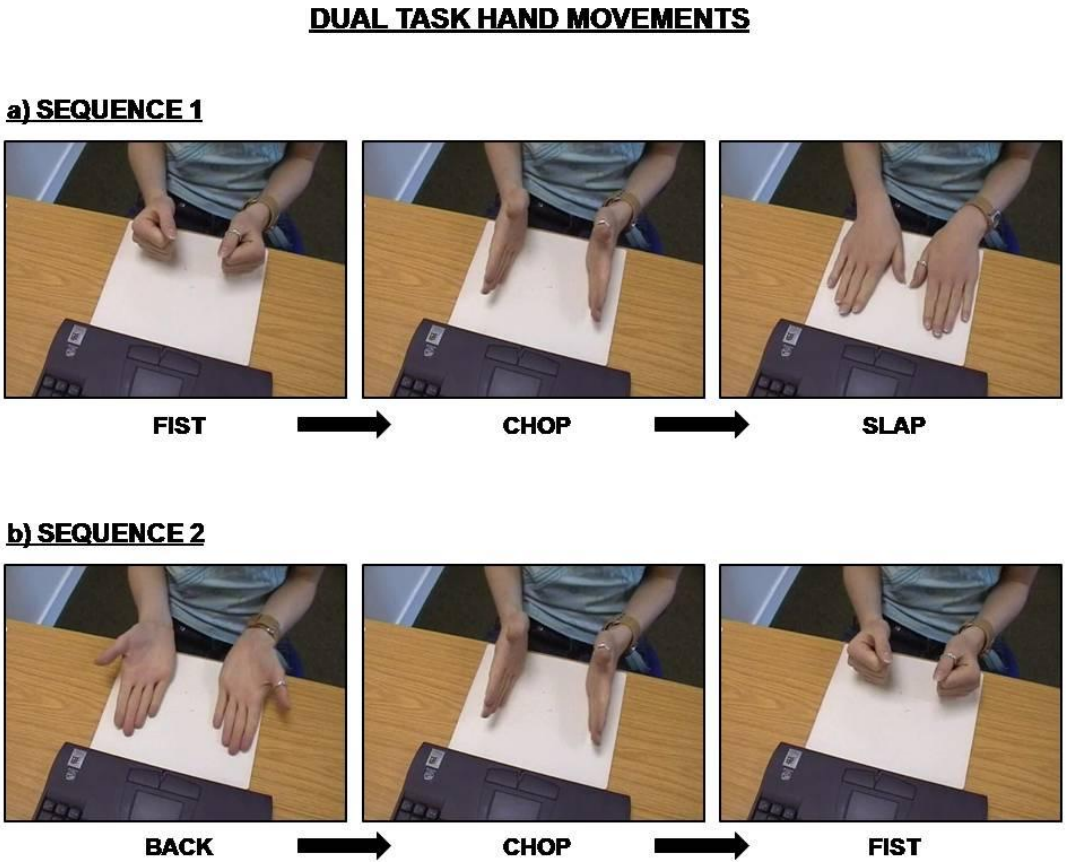


Figure 3.2 Dual task hand movement sequences: a) sequence 1 and b) sequence 2.

3.2.5.4 Filled Retention Period Task

A 10 minute task was completed following word display, in order to prevent rehearsal of the items. Participants were given several sheets of long multiplications to do by hand. This filler task has previously been successfully employed in this role (Sünram-Lea et al., 2008).

3.2.6 Procedure

Participants were visually isolated and wore ear defenders to limit noise distractions whilst being tested in groups of up to 5, in a small lab. There was a minimum washout period of 48 hours between study visits.

On each of the 4 study visits, participants presented to the lab between 8.30 am and 9.30 am, following a minimum fast of 12 hours during which only water was consumed.

Compliance with fasting instructions was checked verbally and through baseline blood glucose measurements. Participants start times were staggered such that participants only entered the room during the filler task to minimise distractions during testing. Prior to completing the first test session, consent was sought and initial screening completed. Participants were also fully briefed on all of the tasks that they would be asked to complete. On screen instructions guided participants through the tasks they were to complete in order and to reiterate the previously delivered verbal and written instructions for each task. If at any point the participant was unsure of what was being asked of them, they were to seek clarification from the experimenter. Upon presentation to the lab prior to a high effort dual task visit, participants were briefed on how to complete the dual task, prior to the study day being commenced.

Following a baseline measurement of blood glucose, participants consumed the drink and rested for 15 minutes to allow for absorption. Time point 0 minutes was locked to participants finishing the drink. Following the 15 minute absorption period, a pre-test blood glucose measurement was taken and testing commenced. Testing was completed in the following order; 1) word display (+/- dual hand movement task), 2) filler task: pen and paper long hand multiplications, and 3) word recognition task. Post-test blood glucose levels were finally assessed (see figure 3.3).

Of the possible 24 treatment/effort orders for the study day conditions, only 20 were used, such that each of the 4 treatment/effort combinations were completed equally across study days, i.e. each condition was completed on the 1st , 2nd, 3rd and 4th study days by 5 participants. Participants were randomly allocated to a set condition order, with no 2 participants completing the conditions in the same order. All stimuli were randomised for each participant, to minimize any practice effects or variation in difficulty affecting performance.

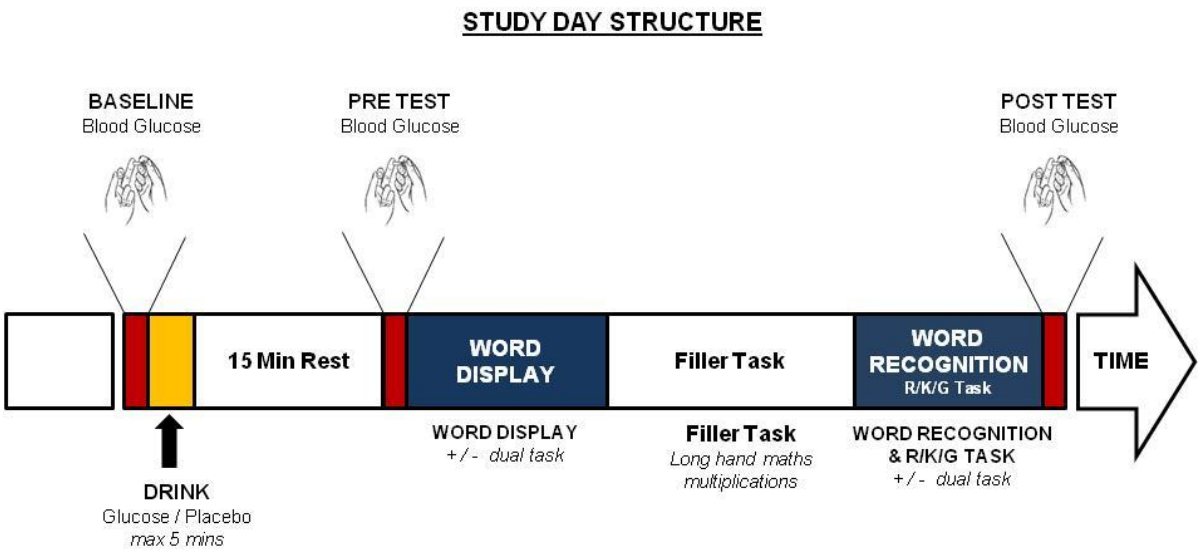


Figure 3.3 A schematic of the study day visit structure.

3.2.7 Statistics

A median split was utilised to group participants into better or poorer glucoregulators on the basis of the area under the curve (AUC) for the glucose low effort visit.

Blood glucose levels on study days were analysed via a 4 way mixed (Time x Treatment x Effort x Glucoregulation) ANOVA.

A four way mixed (Treatment x Effort x Recognition Type x Glucoregulation) ANOVA was used to analyse outcomes from the word recognition task.

Where ANOVA revealed significant findings ($p<0.05$) post hoc pairwise comparisons with Bonferroni correction applied were completed. Only the highest order interaction effects are reported in the text. Lower order effects are indicated in the outcome tables.

3.3 Results

3.3.1 Blood Glucose Levels

Table 3.1 shows the mean and SEM for blood glucose levels with significant effects and interactions.

Table 3.1 Means, SEM and significant effects for circulatory blood glucose levels. Significant effects and interactions are indicated in the final column *(Ef = Effort, Glureg = Glucoregulation, Ti = Time, Tr = Treatment, **p<0.01, ***p<0.005, *****p<0.0005).*

Outcome	Timepoint	Task Effort Level	Glucoregulation Group	*n*=	Glucose			Placebo			Significant Effects & Interactions
					Means	±	SEM	Means	±	SEM	
Blood Glucose Levels	Baseline	High	Better	10	5.24	±	0.15	5.69	±	0.08	Ti ***** Tr ***** Glureg ** Ti x Tr ***** Ti x Ef x Glureg *** Ti x Tr x Ef x Glureg ***
			Poorer	10	5.14	±	0.13	5.01	±	0.14	
		Low	Better	10	5.57	±	0.12	5.56	±	0.19	
			Poorer	10	4.75	±	0.13	5.00	±	0.13	
	Pre-Test	High	Better	10	6.95	±	0.24	5.65	±	0.10	
			Poorer	10	6.15	±	0.21	5.05	±	0.15	
		Low	Better	10	6.28	±	0.13	5.47	±	0.08	
			Poorer	10	6.47	±	0.16	5.10	±	0.12	
	Post-Test	High	Better	10	8.11	±	0.41	5.67	±	0.08	
			Poorer	10	8.33	±	0.34	5.08	±	0.10	
		Low	Better	10	8.14	±	0.24	5.44	±	0.13	
			Poorer	10	8.39	±	0.36	5.07	±	0.18	

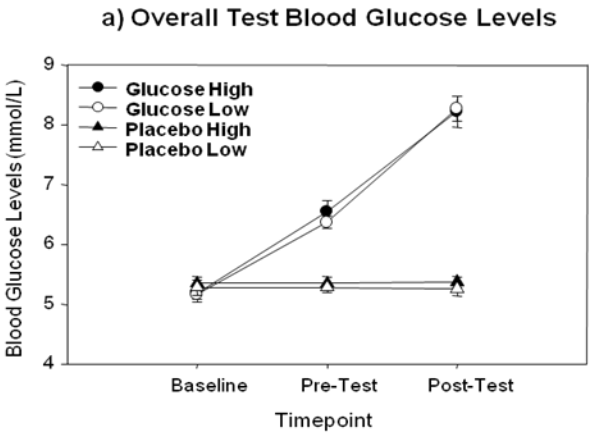


Figure 3.4 Glucose levels; *a)All participants mean glucose levels, and b) Better vs. poorer glucoregulators test glucose levels. (High = high effort dual task, Low = low effort no dual task, see table 3.2 for significant pairwise comparisons for figure b).*

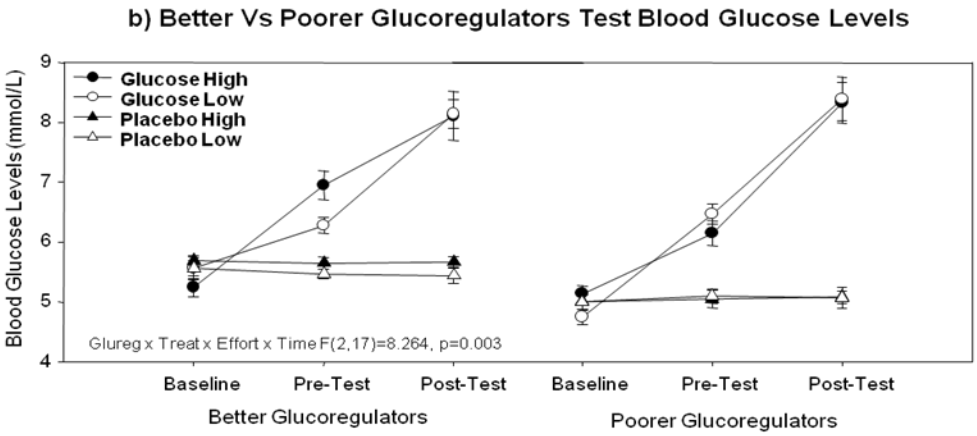


Figure 3.4a above shows the mean overall glucose response curves for each treatment / effort condition, with figure 3.4b showing the test glucose levels for the better and poorer glucoregulators respectively, as defined by the AUC median split for the glucose low effort visit. A one way ANOVA showed better glucoregulators AUC was significantly smaller than poorer glucoregulators ($F_{1,18}=24.641$, $p<0.0005$, $r=0.760$).

For blood glucose levels there was a significant four way treatment x effort x glucoregulation x time interaction ($F_{2,17}=8.264$, $p=0.003$, $r=0.572$), see figure 3.4b. Post hoc pairwise comparisons revealed several significant findings, which are summarised in table 3.2. Interestingly, the better glucoregulators showed higher baseline circulatory glucose than poorer glucoregulators on all visits except for prior to glucose with high effort. At pre-test following glucose, better glucoregulators had significantly higher circulatory glucose levels on the high effort than low effort visit.

Table 3.2 Significant pairwise comparisons for the 4 way blood glucose treatment x effort x glucoregulation x time interaction (t values and p values are indicated).

Condition / Group	Blood Glucose Pairwise Difference	t(17)=	P Value
Better Glucoregulators, Glucose, High Effort	Baseline < Pre-Test	7.814	<0.001
	Baseline < Post-Test	7.150	<0.001
	Pre-Test < Post-Test	2.796	0.036
Better Glucoregulators, Glucose, Low Effort	Baseline < Pre-Test	5.230	<0.001
	Baseline < Post-Test	8.492	<0.001
	Pre-Test < Post-Test	5.749	<0.001
Poorer Glucoregulators, Glucose, High Effort	Baseline < Pre-Test	4.341	0.001
	Baseline < Post-Test	7.984	<0.001
	Pre-Test < Post-Test	5.269	<0.001
Poorer Glucoregulators, Glucose, Low Effort	Baseline < Pre-Test	12.695	<0.001
	Baseline < Post-Test	12.034	<0.001
	Pre-Test < Post-Test	5.695	<0.001
Baseline, Glucose, Low Effort	Better > Poorer Glucoregulators	4.658	<0.001
Baseline, Placebo, High Effort	Better > Poorer Glucoregulators	4.186	0.001
Baseline, Placebo, Low Effort	Better > Poorer Glucoregulators	2.455	0.024
Pre-Test, Glucose, Low Effort	Better > Poorer Glucoregulators	2.544	0.02
Pre-Test, Placebo, High Effort	Better > Poorer Glucoregulators	3.436	0.003
Pre-Test, Placebo, Low Effort	Better > Poorer Glucoregulators	2.660	0.016
Post-Test, Placebo, High Effort	Better > Poorer Glucoregulators	4.455	<0.001
Baseline, High Effort, Better Glucoregulators	Placebo > Glucose	2.671	0.016
Pre-Test, High Effort, Better Glucoregulators	Glucose > Placebo	6.053	<0.001
Pre-Test, High Effort, Poorer Glucoregulators	Glucose > Placebo	5.155	<0.002
Pre-Test, Low Effort, Better Glucoregulators	Glucose > Placebo	5.963	<0.003
Pre-Test, Low Effort, Poorer Glucoregulators	Glucose > Placebo	10.166	<0.004
Post-Test, High Effort, Better Glucoregulators	Glucose > Placebo	6.700	<0.005
Post-Test, High Effort, Poorer Glucoregulators	Glucose > Placebo	8.917	<0.006
Post-Test, Low Effort, Better Glucoregulators	Glucose > Placebo	7.214	<0.007
Pos-Test, Low Effort, Poorer Glucoregulators	Glucose > Placebo	8.890	<0.008
Pre-Test, Glucose, Better Glucoregulators	High Effort > Low Effort	2.990	<0.009

3.3.2 Word Recognition

Table 3.3 shows the mean and SEM for the word recognition task outcomes, with the significant effects also indicated.

Table 3.3 Mean scores and SEM for the word recognition task outcomes. Significant effects and interactions are indicated in the final column (*Ef = Effort, Glureg = Glucoregulation, Rtype = Recognition Type, Tr = Treatment, *p<0.05, **p<0.01, *****p<0.0005).*

Outcome	Response Type	Task Effort Level	Glucoregulation Group	*n*=	Glucose			Placebo			Significant Effects & Interactions
					Means	±	SEM	Means	±	SEM	
% Correct	Old	High	Better	10	47.75	±	3.93	47.25	±	4.65	Ef ***** Rtype ** Rtype x Ef ***** Tr x Ef *
			Poorer	10	53.50	±	3.67	49.25	±	1.75	
		Low	Better	10	66.75	±	5.32	70.25	±	4.99	
			Poorer	10	75.50	±	2.98	75.00	±	5.03	
	New	High	Better	10	66.00	±	3.73	62.75	±	3.56	
			Poorer	10	71.00	±	3.97	67.75	±	4.39	
		Low	Better	10	69.50	±	4.26	75.25	±	4.62	
			Poorer	10	79.75	±	3.81	81.00	±	3.34	
Correct RT	Old	High	Better	10	1887	±	283	1629	±	206	Rtype * Rtype x Ef * Tr x Ef x Glureg *
			Poorer	10	1563	±	133	1684	±	127	
		Low	Better	10	1590	±	196	1725	±	227	
			Poorer	10	1344	±	67	1362	±	79	
	New	High	Better	10	1648	±	238	1399	±	127	
			Poorer	10	1418	±	104	1502	±	157	
		Low	Better	10	1437	±	199	1678	±	247	
			Poorer	10	1486	±	121	1288	±	100	
Incorrect RT	Old	High	Better	10	1813	±	274	1469	±	123	Ef * Rtype ** Rtype x Eff * Tr x Ef x Glureg *
			Poorer	10	1422	±	106	1613	±	157	
		Low	Better	10	1560	±	187	1759	±	230	
			Poorer	10	1796	±	185	1437	±	95	
	New	High	Better	10	1855	±	230	1800	±	275	
			Poorer	10	1634	±	170	1774	±	176	
		Low	Better	10	1909	±	373	2329	±	319	
			Poorer	10	1996	±	284	2036	±	169	
% R/K/G Responses (Correct Recognition)	Remember	High	Better	10	22.35	±	7.18	33.42	±	8.12	Rtype x Ef *****
			Poorer	10	22.16	±	3.68	23.60	±	4.51	
		Low	Better	10	52.46	±	8.58	49.28	±	9.37	
			Poorer	10	44.57	±	4.57	54.25	±	5.42	
	Know	High	Better	10	24.68	±	3.59	22.53	±	4.47	
			Poorer	10	27.77	±	3.74	29.21	±	3.61	
		Low	Better	10	29.31	±	7.31	30.68	±	7.87	
			Poorer	10	34.52	±	3.78	23.72	±	3.24	
	Guess	High	Better	10	52.97	±	8.27	44.05	±	7.67	
			Poorer	10	50.07	±	6.37	47.19	±	4.84	
		Low	Better	10	18.23	±	4.84	20.04	±	4.65	
			Poorer	10	20.91	±	3.98	22.03	±	4.85	
% R/K/G Responses (Incorrect Recognition)	Remember	High	Better	10	13.46	±	6.11	21.35	±	6.98	Rtype *****
			Poorer	10	9.79	±	3.97	15.73	±	4.29	
		Low	Better	10	22.14	±	7.52	20.84	±	9.61	
			Poorer	10	9.92	±	4.47	6.87	±	2.83	
	Know	High	Better	10	19.77	±	5.83	17.60	±	4.94	
			Poorer	10	13.77	±	5.00	16.32	±	6.73	
		Low	Better	10	29.97	±	8.87	23.19	±	5.93	
			Poorer	10	15.96	±	4.25	17.92	±	8.97	
	Guess	High	Better	10	66.76	±	9.27	61.06	±	9.59	
			Poorer	10	76.44	±	6.61	67.95	±	8.78	
		Low	Better	10	47.90	±	11.50	55.97	±	11.31	
			Poorer	10	64.12	±	8.83	75.21	±	10.07	
Correct Recognition RT by RKG	Remember	High	Better	10	1304	±	414	1456	±	312	Rtype *****
			Poorer	10	1276	±	203	1382	±	140	
		Low	Better	10	1371	±	168	1715	±	289	
			Poorer	10	1239	±	130	1190	±	50	
	Know	High	Better	10	1786	±	238	1507	±	189	
			Poorer	10	1511	±	152	1572	±	165	
		Low	Better	10	1543	±	179	2250	±	614	
			Poorer	10	1288	±	97	1575	±	169	
	Guess	High	Better	10	1988	±	303	1624	±	121	
			Poorer	10	1674	±	159	1880	±	171	
		Low	Better	10	2426	±	754	1733	±	275	
			Poorer	10	1767	±	153	1723	±	111	
R/K/G Decision RT (Correct Recognition)	Remember	High	Better	7	1546	±	756	602	±	110	Rtype x Ef *
			Poorer	9	683	±	171	963	±	298	
		Low	Better	7	501	±	98	644	±	208	
			Poorer	9	589	±	83	446	±	79	
	Know	High	Better	7	1023	±	386	754	±	164	
			Poorer	9	641	±	156	594	±	128	
		Low	Better	7	599	±	152	824	±	273	
			Poorer	9	633	±	131	497	±	87	
	Guess	High	Better	7	701	±	172	852	±	158	
			Poorer	9	560	±	151	522	±	85	
		Low	Better	7	1088	±	576	721	±	211	
			Poorer	9	556	±	125	429	±	31	

For correctly recognised items there was a treatment x effort interaction ($F(1,18)=4.593$, $p=0.046$, $r=0.451$), with a greater proportion of correct responses made following low effort than high after glucose ($t(18)=5.476$, $p=<0.0005$) and placebo ($t(18)=7.997$, $p<0.0005$), see figure 3.5a. For correctly recognised items there was also an effort x recognition type interaction ($F(1,18)=18.862$, $p<0.0005$, $r=0.715$), with no difference between old and novel item recognition following low effort, but decreased recognition of old ($t(18)=7.674$, $p<0.0005$) and novel ($t(18)=4.664$, $p<0.0005$) items following high effort. High effort also lead to fewer correct recognitions of old items than novel items ($t(18)=4.593$, $p<0.0005$), see figure 3.5b.

For correct ($F(1,18)=5.159$,$p=0.036$, $r=0.472$) and incorrect ($F(1,18)=7.710$, $p=0.012$, $r=0.548$) recognition reaction times there was a recognition type x effort interaction. Correct recognition reaction times were the same for old and novel items following low effort, and novel items following high effort. Correct recognitions of old items were slower following high effort than low ($t(18)=2.118$, $p=0.048$) and slower than novel items also following high effort ($t(18)=3.371$, $p=0.003$), see figure 3.5c. Incorrect recognitions of novel items were significantly slower following low effort than high ($t(18)=3.442$, $p=0.003$), and slower than old items following low effort ($t(18)=3.591$, $p=0.002$), see figure 3.5d.

For correct ($F(1,18)=6.202$,$p=0.023$, $r=0.506$) and incorrect ($F(1,18)=5.211$, $p=0.035$, $r=0.474$) recognition reaction times there was a treatment x effort x glucoregulation interaction. Correct recognitions were made slower by better glucoregulators after low effort with placebo than glucose ($t(18)=2.160$, $p=0.045$), with poorer regulators giving slower correct recognitions following placebo high effort than low ($t(18)=2.140$, $p=0.046$), see figure 3.5e. Better regulators made slower incorrect recognitions after placebo low effort then high ($t(18)=2.248$, $p=0.025$), with poorer regulators giving slower incorrect recognitions after glucose low effort than high ($t(18)=2.247$, $p=0.037$), see figure 3.5f.

The proportion of remember/know/guess responses following correct recognition showed an effort x response type interaction $F(2,17)=45.655$, $p<0.0005$, $r=0.854$). Following high effort, more guess recognitions were made than remember ($t(17)=2.760$, $p=0.039$), and know ($t(17)=4.105$, $p=0.002$). Following low effort more remember recognitions were made than guess ($t(17)=4.356$, $p=0.001$). Significantly more remember recognitions were made following low than high effort ($t(170=7.602$, $p<0.0005$) with more guess recognitions made following high effort than low ($t(17)=8.272$, $p<0.0005$), see figure 3.6a. For the proportion of incorrectly recognised items, there was a main effect of response type for the number of remember/know/guess responses ($F(2,17)=17.645$, $p<0.00005$, $r=0.714$),

with more guess responses given than remember (t(17)=5.926, p<<0.0005) and know (t(17)-5.939, p<0.0005) responses, see figure 3.6b.

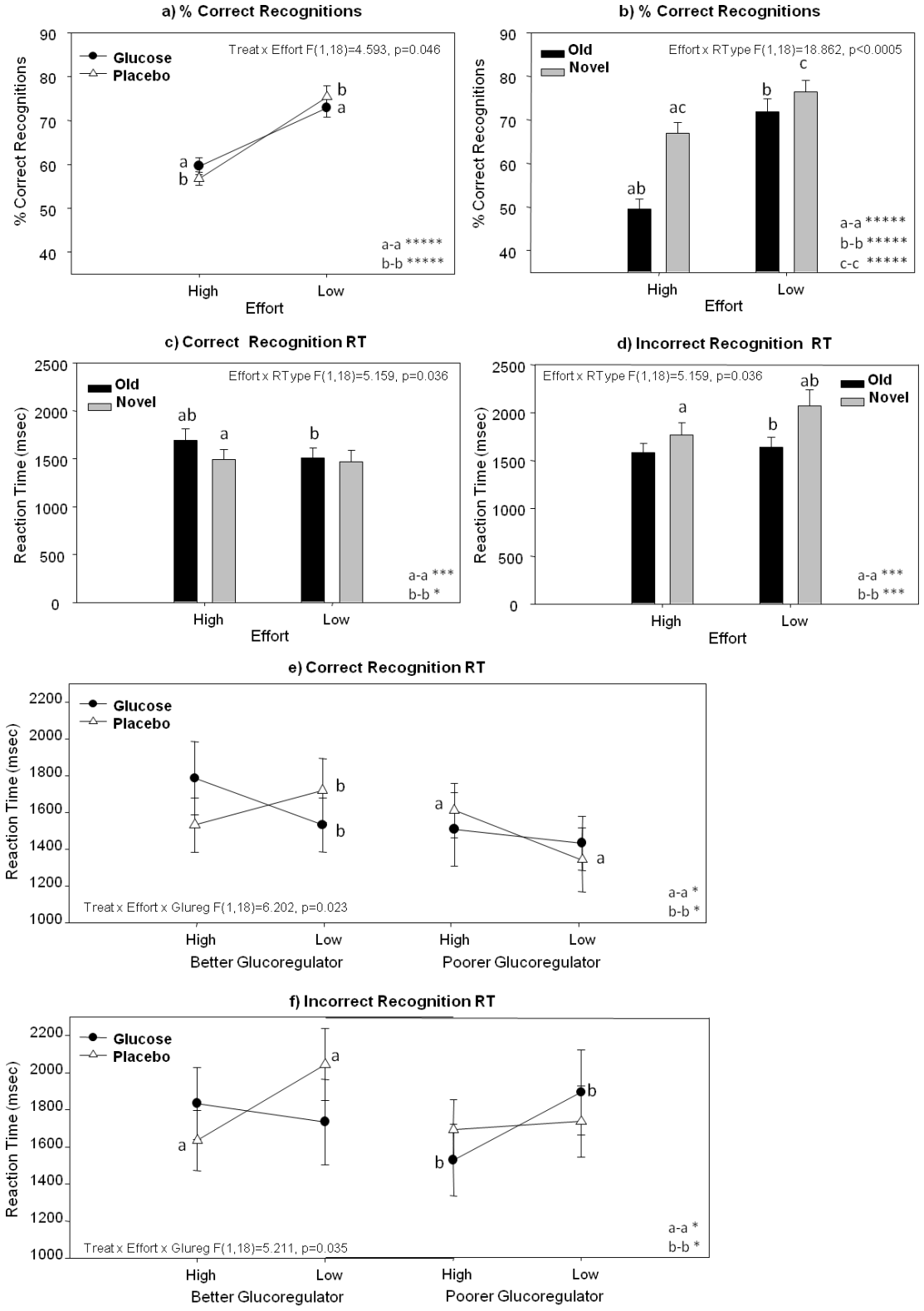


Figure 3.5 Recognition interactions*; a) % Correct Effort x Treatment, b) % Correct Effort x Response Type, c) Correct RT Effort x Response Type, d) Incorrect RT Effort x response Type, e) Correct RT Treatment x Effort x Glucoregulation and f) Incorrect Treatment x Effort x*

Glucoregulation. (High = High effort dual task, Low = low effort no dual task, see keys on figures for pairwise significances).

For reaction times to give correct recognitions by remember/know/guess responses, there was a main effect of response type ($F(2,17)=16.552$, $p<0.0005$, $r=0.702$), with guess responses being made slower than remember ($t(17)=5.519$, $p<0.0005$) and know ($t(17)=2.832$, $p=0.033$) responses, see figure 3.6c.

Following a correct recognition, the reaction time to make a remember/know/guess decision showed a response type x effort interaction ($F(2,13)=3902$, $p=0.047$, $r=0.480$). Pairwise comparisons revealed remember responses were made slower following high effort than low effort ($t(13)=2.553$, $p=0.023$), see figure 3.6d.

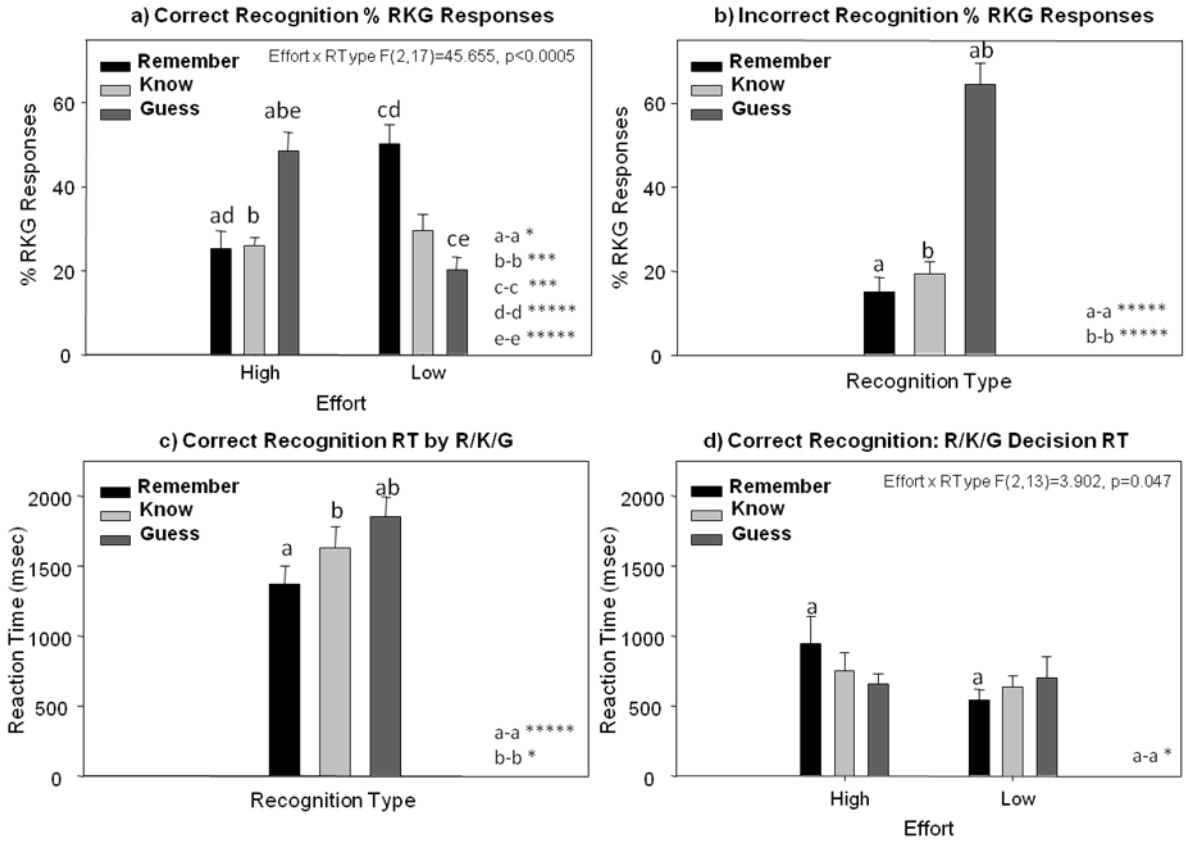


Figure 3.6 Recognition type (R/K/G) effects and interactions; *a) % RKG Responses from correct recognitions; effort x response type, b) % RKG responses from incorrect recognitions; effort effect, c) Correct recognition RT for RKG responses; response type effect, and d) RKG decision time following correct recognition RT; effort x response type. (High = High effort dual task, Low = low effort no dual task, R = Remember, K = Know, G=Guess response type, see keys on figures for pairwise significances).*

3.4 Discussion

3.4.1 Summary of Main Findings

This chapter aimed to investigate whether the glucose facilitation effect on memory is preferentially targeting tasks that are dependent on the hippocampus. The impact of glucoregulatory control on task performance and increased effort was also investigated. Increased recollection (remember) recognitions with no change in familiarity (know) recognitions following a glucose load, would indicate that that increased circulatory glucose was preferentially targeting the hippocampus. The evidence within this chapter did not support this postulation, with no effect of a glucose drink on the type of recognitions that were made. Strong effort effects were found throughout the recognition outcomes, with the high effort manipulation impairing accuracy and reducing the proportion of 'remember' recognitions. Limited evidence was presented of a treatment by glucoregulation interaction influencing recognition performance, with better regulators seeming to benefit from the glucose load. Correct recognitions were made faster by better glucoregulators following glucose than placebo, although the effects observed are not clear.

3.4.2 Blood Glucose

Median splits on the AUC during the glucose with no secondary task visit, were conducted to form two groups; better glucoregulators (smaller AUC) and poorer glucoregulators (larger AUC). A one way ANOVA revealed that the AUCs were significantly different, which suggests that this grouping does allow interpretation of the findings to be discussed in terms of better and poorer glucoregulators. Participants presented with fasting glucose levels within normal fasting range, although the better regulators presented with significantly higher baseline levels for all visits other than glucose with high effort.

A highly significant 4 way (treatment x effort x time x glucoregulation) interaction revealed some interesting findings. As expected the glucose drink successfully raised circulatory glucose levels in both better and poorer regulators. However, a finding that was not expected was that prior to the high effort task (at pre-test), better regulators had higher circulating glucose levels than prior to low effort. This finding was unique to the glucose with high effort (dual task) visit. Following the baseline measures, participants were

aware of whether they would be required to complete the dual task on that visit (the camera and tripod were set up on the desk and the experimenter re-briefed them on the hand movements). This finding may indicate that better glucoregulators are better able to mobilise energy processes in anticipation of an imminent (and expected) increase in demanding. This effect was not seen for poorer regulators. This increased circulating glucose may account for any performance facilitation in better regulators, as additional resources are already in place prior to embarking on demanding tasks. A similar effect was also seen in better regulators prior to high effort with placebo, although this did not reach significance. As poorer regulators did not display this effect at all (glucose levels were actually slightly lower at pre test for glucose high effort than low, although not significantly), they may encounter restricted resource availability during the high effort task.

At post-dose (20 min after the high/low effort manipulation had been completed), no observable differences in blood glucose were apparent between high and low effort conditions. This is in contrast to previous literature which has observed reduced circulatory blood glucose following mentally demanding tasks (Donohoe and Benton, 1999b, Fairclough and Houston, 2004, Scholey et al., 2001, Scholey et al., 2006). Previous works that have detected this decrease have used longer duration intense tasks (Donohoe and Benton, 1999b (20 min), Fairclough and Houston, 2004 (15, 30 and 40 min), Scholey et al., 2001 (5 min)) with blood glucose measured immediately post task. The high demand component of this task lasted for only 2 min with the next glucose measurement taken approximately 18 min later. It is likely that any reduction in glucose caused by the dual task was no longer detectable, as levels had recovered prior to post-test measurements. It is also possible that due to the short duration of the high effort component, it was not intense enough to cause a detectable decrease in circulatory glucose.

3.4.3 Word Recognition

The primary measure in this chapter was the distribution of recollection (remember) and familiarity (know) responses and the potential effect of glucose and glucoregulation on these factors. It was hypothesised that raising circulatory glucose would facilitate recollection should the hippocampal domain be being specifically targeted. Facilitation of both recollection and familiarity by glucose in the high demand manipulation would be observed should task demand be the most important determinant for glucose facilitation.

An effort x response type interaction demonstrated that the introduction of a highly demanding dual task at encoding did impact upon the distribution of recognition types subsequently made. Whilst in high and low effort, the proportion of familiarity responses remained at a comparable level, high effort significantly decreased the number of recollection responses with an associated rise in guess responses. In low effort, a greater proportion of recollection responses were made with a subsequent decrease in guess responses. Following high effort the proportion of recollection and familiarity responses were similar, whereas following low effort significantly more recollection responses were made. The finding of decreased correct recognition in conjunction with a greater reduction of recollection recognition following high effort, closely match the effects seen in previous literature utilising divided attention during the remember/know paradigm (Gardiner and Parkin, 1990, Mangels et al., 2001, Parkin et al., 1995, Yonelinas, 2001, Yonelinas, 2002). However, no mediating effect of a glucose load or glucoregulation was detected in this study, which suggests that increased circulatory blood glucose and the associated physiological effects on insulin etc, do not mediate recollection and familiarity recognition. This is in contrast to Sünram-Lea et al (2008) who found evidence of glucose preferentially targeting enhancement of recollection recognition, and Smith et al. (2009b) who found glucose facilitation of recollection and familiarity recognition. It should again be highlighted that the designs and methodologies of these studies are not directly comparable, for example Sünram-Lea et al. gave the word list auditorily rather than visually, which could have influenced recognition outcomes. Taken in isolation, the data from this outcome measure suggests that glucose is not facilitating recognition memory, with no differing responses to glucose dependent upon glucoregulation or effort manipulations. Consequently no inferences can be made as to domain (demand approach or domain specific) targeted by glucose facilitation of memory. However, when the overall accuracy and response times are considered, there is evidence that treatment and glucoregulation are impacting upon recognition.

The increased dual task effort reduced accuracy during the recognition phase, with decreased accuracy following high effort for both glucose and placebo. The dual task reduced recognition of old items down to chance levels (49.4%) compared to over 71.9% accuracy in the absence of a dual task. Accurate identification of novel items was also decreased following high effort (from 76.4% to 66.9%). Whilst the difference between novel and old item recognition was not significantly different in the low effort condition, following high effort recognition of old items was significantly lower than correct identification of novel items. These findings indicate that the high effort manipulation successfully induced a performance deficit in recognition. As neither treatment nor levels of glucoregulation were found to differentially effect overall accuracy following high or low

effort, should any glucose effects be operating on this recognition task, they are not observable when considering overall accuracy.

Treatment x effort x glucoregulation interactions for correct and incorrect recognition response times, were also observed. Better glucoregulators were faster to make correct recognitions following glucose than placebo in the low effort condition, whereas poorer glucoregulators were faster to make correct recognitions having consumed placebo in the low rather than high effort condition. Incorrect recognitions were made faster by better glucoregulators after placebo when completing the high rather than low effort condition, whereas poorer regulators were faster following glucose and high effort than glucose and low effort. The implications of these findings are unclear, but recognition reaction times do seem to respond differently to treatment and effort dependent upon an individual's glucoregulation. Better regulators seem to benefit from facilitation by glucose in the form of faster correct recognitions, but only during low effort. Poorer regulators do not show any such glucose facilitation, but do show impairments through high effort after placebo via slower recognitions. For incorrect recognition, better regulators following placebo were faster to give incorrect responses following high effort than low, a pattern that was replicated by poorer regulators following glucose not placebo. This may suggest that response times in poorer regulators (at least for incorrect recognitions), are brought into line with better regulators following raised circulating glucose levels.

Response times were not reported by Sünram-Lea et al. (2008), but Smith et al. (2009b) found glucose to speed response times relative to placebo. Smith et al. (2009b) did not assess glucoregulation, but limited support for a glucose facilitation in speeding recognition response times is found in this study. As no main effect of treatment was found, this suggests that such an effect is dependent upon levels of glucoregulation. Smith et al. used adolescents who (presumably) benefit from better glucoregulation, subsequently these findings from this study do support Smith et al.'s findings.

Effort x response type (old / novel) interactions, were found for correct and incorrect recognition response times. The response times for correct recognitions were slower for old items following high effort, but did not differ for other conditions. Slower reaction times for incorrectly identified novel items following low effort were observed, with no other conditions differing significantly. No main effect for response type was found, and the results presented for this study do not support Smith et al's (2009b) findings that responses times are slower for old rather than novel items.

As such it is possible that while glucose and glucoregulation may be exerting an influence on recollection and / or familiarity recognition, although the effects may be too small to reach significance here.

3.4.4 Limitations

The methodology utilised in this chapter to categorise participants as better or poorer glucoregulators is confounded. Glucoregulation is implied from rise in circulatory blood glucose during the low effort study visit. During this period participants are engaged in several cognitive tasks which may influence the circulatory glucose levels. The cognitive demands placed on participants inevitably influence neuronal uptake of glucose, as such an individual's levels of glucoregulation is not solely mediating glucose levels over the testing period. As randomisation was employed to determine treatment/effort condition completion order, participants may be differentially habituated to the lab settings, which in turn may influence anxiety and stress states, which have been shown to interact with glucose facilitation (Smith et al., in press). Additionally the 25 g glucose dose administered here (in conjunction with flavouring), whilst found to be effective in eliciting facilitation, does not represent an appropriate quantity to properly assess glucoregulation. As such the causality of glucose levels during the glucose low effort condition, may not be reliably reflecting a true indication of glucoregulatory control. In order to eliminate this, an Oral Glucose Tolerance Test (OGTT) will be employed for future studies.

3.4.5 Conclusion

The conclusions drawn from this study are tentative, but suggest that glucose and glucoregulation may influence both familiarity and recollection recognition, with limited support presented for the previous literature. The facilitations observed seem to be confined to recognition response times, with better glucoregulators benefiting from faster correct responses. Whilst no conclusive treatment or glucoregulation influences were observed for the different types of recognitions made, it is likely that any effects were masked by the strong effort effects throughout on performance recognition. The introduction of a dual task (along with other methodological differences) may account for the conflicting evidence presented here. No firm assertions can be drawn from the evidence presented as to whether glucose preferentially targets the hippocampal domain or task demand. As recognition is not a robustly facilitated task via glucose administration, the remaining chapters will avoid utilising this task as the primary outcome

in order to maximise task sensitivity to manipulations. Future chapters in this thesis address the methodological limitations encountered here (e.g. measurement of glucoregulation) and assess whether potential facilitation of glucose and interaction with glucoregulation are targeting different phases of memory formation (encoding, consolidation and retrieval).

CHAPTER 4. AN EVALUATION OF THE IMPACT OF GLUCOREGULATORY CONTROL AND GLUCOSE FACILITATORY EFFECTS ON ENCODING EFFICIENCY, VIA THE ITEM METHOD DIRECTED FORGETTING PARADIGM.

4.1 Introduction

While chapter 3 investigated the potential glucose facilitation and glucoregulation effect on retrieval processes using the 'remember/know' paradigm, this chapter examined encoding processes, with particular reference to encoding efficiency. The evidence from chapter 3 was not clear, but tentatively suggested that glucose may mediate performance differently in better and poorer glucoregulators, as better regulators seemingly benefited from speeded correct recognitions following glucose, but only in the low effort condition. Highly significant effort effects were observed throughout the memory retrieval outcomes in chapter 3, which may have obscured any treatment effects. As the high effort dual task manipulation is employed during the encoding stage (as is common in this research area; see section 1.3.5), it seems likely that the encoding phase of memory may be specifically targeted by the facilitating effect of glucose, with glucoregulation mediating the effect.

Efficient memory processes require not only the efficient recall of relevant items or events from memory, but also the effective forgetting of irrelevant, out dated or intrusive information (Johnson, 1994). Inabilities to forget undesirable/intrusive memories can lead to serious daily disadvantages as found with ageing (Lustig et al., 2001, Zacks et al., 1996) and disorders such as obsessive compulsive disorders and post-traumatic stress (Cottencin et al., 2008, Cottencin et al., 2006). Explicit cues are used in deciding which information to forget or disregard (Nowicka et al., 2009a). Directed forgetting (DF) is a paradigm whereby the participants are required to intentionally forget specified items. DF leads to the robust finding that fewer items designated as "to be forgotten" (TBF) are recalled than items designated as "to be remembered" (TBR) (Hourihan and Taylor, 2006). This finding has been replicated across many studies over the last 30 years (e.g. Bjork and Woodward, 1973, Hourihan and Taylor, 2006, MacLeod, 1998, Sego et al., 2006, Woodward et al., 1974). A key note to mention is that the forgetting of TBF items is not due to these items actively being withheld during the recall phase. Macleod (1999) offered a financial incentive to participants on the recall of TBF items, yet this did not prompt an increase in the TBF items recalled.

There are two versions of the directed forgetting paradigm; the list method and item method. The general consensus in the literature being, that these two versions tap into different cognitive mechanisms, manifesting themselves at either encoding or retrieval (Basden et al., 1993, Sego et al., 2006). The list method involves the presentation of the TBR and the TBF words in separate lists, with the forget cue typically given following the initial list. Participants are unaware that they will be informed they can forget the items from the initial list, until after the list has been presented, as such all items may undergo the processing allowing elaborate encoding to occur. This approach is believed to evoke retrieval inhibition processes, with the forget instruction eliciting retrieval inhibition for the items in the list preceding the forget instruction, resulting in the decreased recall of items from the initial TBF list. Support for this explanation of the cognitive mechanism is gleaned by the lack of directed forgetting displayed during a recognition task. Geiselman (1983) found that directed forgetting was eradicated in the list version of the directed forgetting task when a recognition task was utilised (in which release from retrieval inhibition is achieved via the presentation of the items).

When the item method of directed forgetting is utilised, the remember or forget cue is given immediately after each item, in a randomised order. The effectiveness of the forget cue is shown by decreased recall of TBF items, in conjunction with increased successful recall of TBR items. The differences in recall for TBR and TBF items, is believed to stem from the differential encoding of these items. Having been presented with an item, participants 'hold off' elaborate encoding/processing of the word until they are cued to remember it. This more extensive processing of TBR items accordingly leads to greater encoding of TBR words than TBF words (Vonk and Horton, 2006). Imaging studies investigating the item method of directed forgetting have provided evidence that it is increased inhibition of elaborate encoding of TBF items that generate the increased forgetting of these items. Wylie et al. (2008) utilising functional Magnetic Resonance Imaging (fMRI) found that intentional forgetting depends on neural structures distinct from those involved in unintentional forgetting, with increased activity in the hippocampus and superior frontal gyrus for intentionally rather than unintentionally forgotten items. Increased positivity in evoked response potential (ERP) post forget cue in the frontal and prefrontal areas, with larger positivity in the parietal area following a remember cue, suggest that frontal and prefrontal activity serves to limit encoding and parietal activity (Hsieh et al., 2009, Paz-Caballero et al., 2004). Qualitatively different activation patterns at recognition between correctly recognised TBR and TBF items, also suggests differential initial encoding (Nowicka et al., 2009b, Ullsperger et al., 2000), although the authors are reluctant to make firm assertions as retrieval inhibition may also be exerting an influence.

This chapter utilised the item method, as this approach is believed to tap into the encoding control processes, and as such will build upon the results from chapter 3, by investigating whether a glucose load is capable of mediating encoding control processes. Should glucose facilitation of memory be targeting encoding processes, this may be displayed via increased directed forgetting (increased recall of TBR and decreased recall of TBF) being evident in this task following a glucose load.

This thesis is also concerned with examining the effect of glucoregulation on memory in conjunction with a glucose load. As noted in chapter 1, declining levels of glucoregulatory control present with ageing (Awad et al., 2004, Messier et al., 1999). The DF paradigm has been shown to highlight different responses in ageing and young adult populations. It has been suggested that older adults may have deficient inhibitory mechanisms (Hasher et al., 1989), and such deficiencies may lead to a decreased ability to inhibit the encoding of irrelevant/out dated/ or incorrect information (Zacks et al., 1996). Zacks et al. (1996) found that older adults were less able than younger adults to differentially process TBR and TBF items, and as such were more prone to recall TBF items than younger adults, with a smaller overall advantage for recalling TBR then TBF items. This was also replicated using the list method, suggesting deficits in encoding and retrieval inhibition. More recently Dulaney et al. (2004) found a greater magnitude of directed forgetting for young adults than older. Sego et al. (2006) also report directed forgetting in both older and younger adults, but again, younger adults produce a more pronounced effect with greater forgetting of TBF items and greater recall of TBR than older adults, supporting the differential encoding explanation for the age group differences.

Consequently, the deficits in memory encoding in older adults as evidenced by decreased directed forgetting (Dulaney et al., 2004, Sego et al., 2006, Zacks et al., 1996) may in part be attributable to the effects of poorer glucoregulation. If this is the case, better glucoregulators may display increased directed forgetting resulting from increased encoding efficiency compared to poorer regulators. Should glucose facilitate performance on the task, this may present as increased magnitudes of directed forgetting, perhaps preferentially facilitating poorer regulators and/or the highly demanding dual task conditions.

Several methodological changes are employed for this study. Firstly due to the necessary deception that this paradigm employs, a between subjects design is needed. The deception refers to the instructions to the participant that only the TBR cued items need to be remembered for later recall, when in fact they are subsequently asked to recall all items. This then allows the assessment of the actual level of forgetting for the TBF items,

and hence encoding efficiency. As discussed in chapter 3, participants' levels of glucoregulatory control revealed some interesting relationships between glucoregulation and memory performance, however, the methodology used to assess glucose control could be improved. The 'gold standard' for assessing glucoregulation is the Oral Glucose Tolerance Test (OGTT), which is therefore introduced in the experiments used in this chapter and will be used in subsequent studies.

The dual task employed in chapter 3 was highly successful at dividing attention, however, it potentially drew participants visual resources away from the screen presenting the stimulus, with participants reporting difficulties in grasping the concept, particularly on the first high effort visit. Additionally as it was such a prominent factor throughout the analysis, perhaps an alternative task with an appropriate lower demanding dual task counterpart will allow a better interpretation of the demand aspect, particularly in a between subjects design. A verbal serial 3s subtraction task (paced at one subtraction per word presentation) is employed as the high demand dual task, with low demand dual task of verbalising "7 7 7 ", to match the processes required to generate such responses.

This chapter aims to dissociate whether the potentially facilitating effects of glucose are preferentially targeting encoding efficiency, and whether encoding efficiency impairments may be a resultant feature of poor glucoregulatory control. Several hypotheses were tested in this study:

- Better glucoregulators will display greater directed forgetting than poorer regulators, which will be evident via fewer forget items being recalled at immediate and delayed recall. Slower rejections of forget items by poorer glucoregulators during word recognition would also support this. These findings would support the proposal that there are decrements in encoding efficiency in poorer glucoregulators.

- The high demand dual task is expected to decrease overall recall in conjunction with decreasing the magnitude of directed forgetting displayed. This manipulation will induce a performance deficit which, should glucose facilitate encoding efficiency, would reinstate (to some degree) levels of directed forgetting. This prediction may be particularly evident in better glucoregulators who may be performing at a level closer to ceiling performance.

- It is also suggested that poorer glucoregulators maybe more susceptible to facilitation by glucose. Such an effect may be displayed as poorer glucoregulators

levels of directed forgetting being elevated following glucose to a level closer to that displayed by better glucoregulators.

4.2 Materials and Method

4.2.1 Design

A placebo-controlled, double blind, randomised parallel groups design was used. Various cognitive and mood/appetite outcomes were assessed. The variables were two treatment (25 g glucose or placebo) and two effort (high demand dual task or low demand dual task). Participants were randomly allocated to one of four conditions; glucose with high or low demand dual task, or placebo with high or low dual task.

Glucoregulation was assessed using an Oral Glucose Tolerance Test (OGTT) and a median split used to allocate participants to better or poorer glucoregulation groups, on the basis of their evoked glucose at 60 min minus baseline levels from the OGTT. Previous research has shown evoked indices at this time point to be correlated with memory tasks (Messier et al., 2003) and importantly, this glucoregulation index also covers the time-frame of cognitive and mood assessment on study days. As any immediate glucoregulatory responses impacting on performance will be those acting in this time frame.

4.2.2 Participants

Sixty self reported healthy volunteers (28 males, mean age 23.24 yrs, *SD 4.13*) took part in this study which was approved by the Northumbria University Division of Psychology Ethics Committee. Following completion of the study participants received an honorarium of £40. Prior to a participant enrolling into the study, informed consent and screening were completed, ensuring all participants were in good health, free from illicit and recreational drugs including prescription and 'over-the-counter' medications (excluding contraceptives), did not suffer from any metabolic disorders such as glucose intolerance or diabetes, or any allergies that would prevent consumption of the treatments. Of the 60 participants, 6 were smokers (mean 9 cigarettes per day *SD 3.97*). Demographic and morphometric information was recorded including years in education (mean 16.10 yrs, *SD 1.90*), BMI (mean 23.51, *SD 3.14*) and WHR (mean 0.84, *SD 0.10*), see appendix 1.3 for full individual participant characteristics. Prior to each lab visit, participants fasted for a minimum of 12 hours, drinking only water over this period. Food diaries were kept for the 24 hours prior to all visits to aid fasting compliance, see appendix 3.2.

4.2.3 Blood Glucose Levels

Blood glucose levels were monitored using a Reflotron Plus diagnostic instrument and Reflotron test sticks (Roche Diagnostics, Germany), as per chapter 3.

Blood glucose levels were measured via capillary finger prick at baseline, pre-test (15 min post dose) and at post test (~45 min post dose) for test visits. Following completion of the practice session an OGTT was completed with glucose levels measured at Baseline, 30, 60, 90 & 120 min post glucose load.

4.2.4 Treatments

The glucose load for the OGTT was comprised of 75 g glucose in 250ml of water. Test treatments comprised of 25 g glucose (active) or saccharine (placebo), with 20ml Robinsons no added sugar orange cordial, made up to a volume of 200ml with water. Participants were permitted up to 5 minutes in which to consume the drink, with the end of the drink consumption time locked as 0 mins (t=0). Study day treatments were prepared by a disinterested third party in order to ensure the study remained double blind. Drinks were made the evening prior to the participants visit and were kept refrigerated overnight in sealed containers.

4.2.5 Assessment

4.2.5.1 Appetitive and Mood Scales

At baseline, 15 min post dose (pre-test) and completion of test battery (post test, approx 45 min), computerised appetitive and mood scales were completed. Participants rated 'hungry', 'thirsty', 'alert' and 'stressed' levels on a 100 mm visual analogue scale (VAS), by moving an on screen slider to the appropriate position on the scale labelled 'not at all' and 'extremely', on the left and right ends respectively, to indicate their current state for each descriptor. A computerised version of the Bond Lader (Bond and Lader, 1974) was also completed, along with the paper Short Form State Trait Anxiety Inventory (SF STAI). The SF STAI is comprised of 6 items from the original full 16 item STAI (Spielberger, 1983)

and has been verified (Tluczek et al., 2009, Marteau and Bekker, 1992), see appendix 4. Additionally at post test, a paper VAS for 'effortfulness' of the visit was completed.

4.2.5.2 Directed Forgetting Paradigm and Word Display

Forty words were presented on the centre of a screen for 3 seconds, and were immediately replaced with a cue to remember (TBR) the previous word ("RRRRRR") or forget it (TBF) ("FFFFFF") which remained on screen for 1 second, see figures 4.1a-c. This was then replaced by the next word item. Timings vary with the published literature using the item method of DF, these timings were selected as 3 seconds has been shown to be an adequate exposure time in which to encode the items, with a 1 second display adequate in which to produce the DF effect. Twenty items were designated as to be remembered and 20 as to be forgotten. The order of the full word list of 40, was randomised (new randomisation for each participant). Items were selected from two syllable nouns of the Toronto Word Pool (Friendly et al., 1982), with americanised and emotional items avoided so as to avoid confounding factors. During the practice visit, 40 items, also selected from the Toronto Word Pool were displayed for 3 seconds, with a blank screen inter stimulus delay of 1 second.

4.2.5.3 Immediate and Delayed Recall

Participants were presented with on screen instructions requiring them to recall as many of the items from the word display as possible, regardless of whether the word had been followed by a remember or forget cue. This key aspect of the instructions was highlighted to reiterate the importance of it. Participants were given 2.5 minutes and were provided with a pen and paper on which to record their responses.

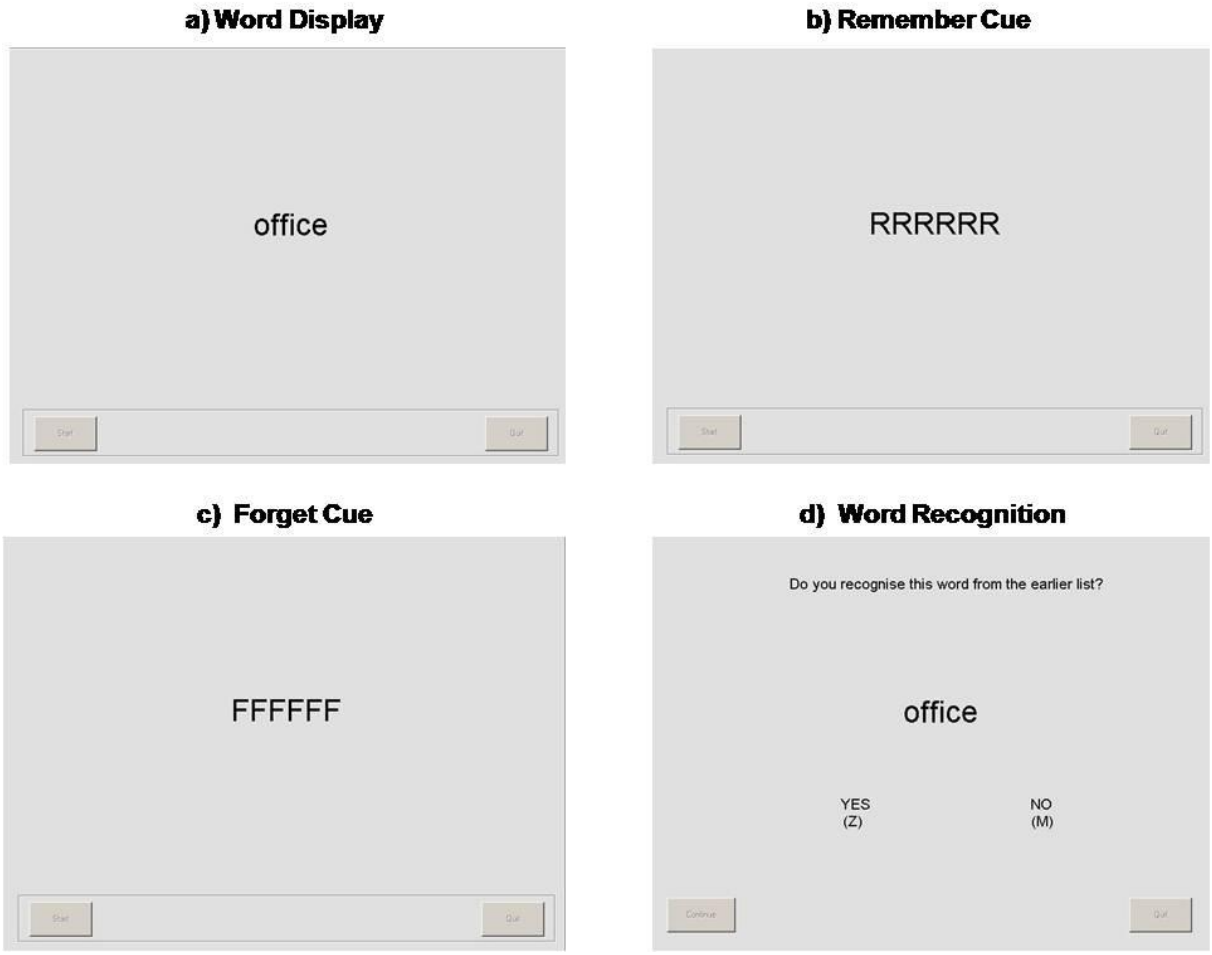


Figure 4.1 On Screen task displays of; *a) Word Display, b) Remember cue, c) Forget cue, and d) Word Recognition Task.*

4.2.5.4 Word Recognition

Eighty words were presented serially consisting of the 40 words originally presented, and 40 additional novel items. Novel items were again selected randomly from the noun section of the Toronto Word Pool, with presentation of all 80 items randomised for each participant.

Words were displayed in the centre of the screen, above which was the question *'Do you recognise this word as one that was shown earlier?'.* Participants were required to respond as quickly and accurately as possible via 'Z' key press for a recognition or 'M' key press for non recognition, by the appropriate index finger, see figure 4.1d.

4.2.5.5 Dual Task

Due to the nature of this paradigm it was necessary to use a non-visual dual task, as this modality is engaged solely in the word display element in line with previous research utilising this paradigm. As such a verbal serial threes subtraction task was employed, which was a modified version of the task originally designed by Hayman (1942). The instruction screen prior to word completion, advised the participants of the starting number (this was 950 for all participants). Participants were required to make a single subtraction of 3 each time a new word was displayed on screen (e.g. the first response would be 947, then for the second word 944 etc). In the case of an error participants were instructed to continue subtracting from the last number spoken. Auditory recordings of the serial subtractions were made and checked for compliance. In the low effort condition, participants were required to verbalise "7 7 7", for each word displayed. During the practice visit participants were instructed to verbalise "1 2 3" for each word displayed. A single beep was sounded at the onset of each word displayed. This allowed the checking of compliance with the instructions to make one subtraction for each word, via the auditory recording.

Participants were advised to complete both tasks to the best of their abilities, with no advice given to prioritise one task over the other.

4.2.5.6 Filled Retention Period Task

A 10 minute task was completed immediately following the repeated cuing phase, in order to prevent rehearsal of items. Participants were given several sheets of long multiplications to do by hand. This filler task was successfully employed in chapter 3.

4.2.6 Procedure

Participants were tested individually whilst wearing ear defenders to limit any noise distractions. All participants were required to fast for 12 hours prior to presenting at the lab, drinking only water during this period. Compliance with fasting instructions was checked verbally, via completion of a food diary for the 24 hour period prior to the visit and by examination of baseline blood glucose levels. Smokers were asked to refrain from smoking on the morning of each visit, until they had completed the sessions.

The study commenced with a practice day starting between 8.30am and 9.30am. The practice visit served to habituate participants to the lab setting and familiarise them with the type of tasks that they were required to complete on the subsequent test visit. Participants were instructed on and asked to complete the SF STAI, the paper VAS and computerised Bond Lader. They then completed a word display task whilst verbalising "1 2 3" each time a new word was displayed, which was recorded. This approximated the dual task that was employed on the second visit. Immediate free recall was then completed. Following this, participants completed a single repetition of verbalised serial 3 subtractions, then serial 7 subtractions. As verbal serial 3 subtractions were employed as the high demand task, this served to ensure participants fully understood and were able to successfully complete this task in the absence of a dual task. The filler task on the test visit was comprised of long hand multiplications, as such a short version of this was completed for 5 minutes, followed by delayed word free recall and the word recognition task. The OGTT was then completed, with baseline blood glucose measured prior to consumption of the 75 g glucose drink. Participants then rested over the subsequent 2 hours, with blood glucose measured at 30 min intervals post dose (see figure 4.2a).

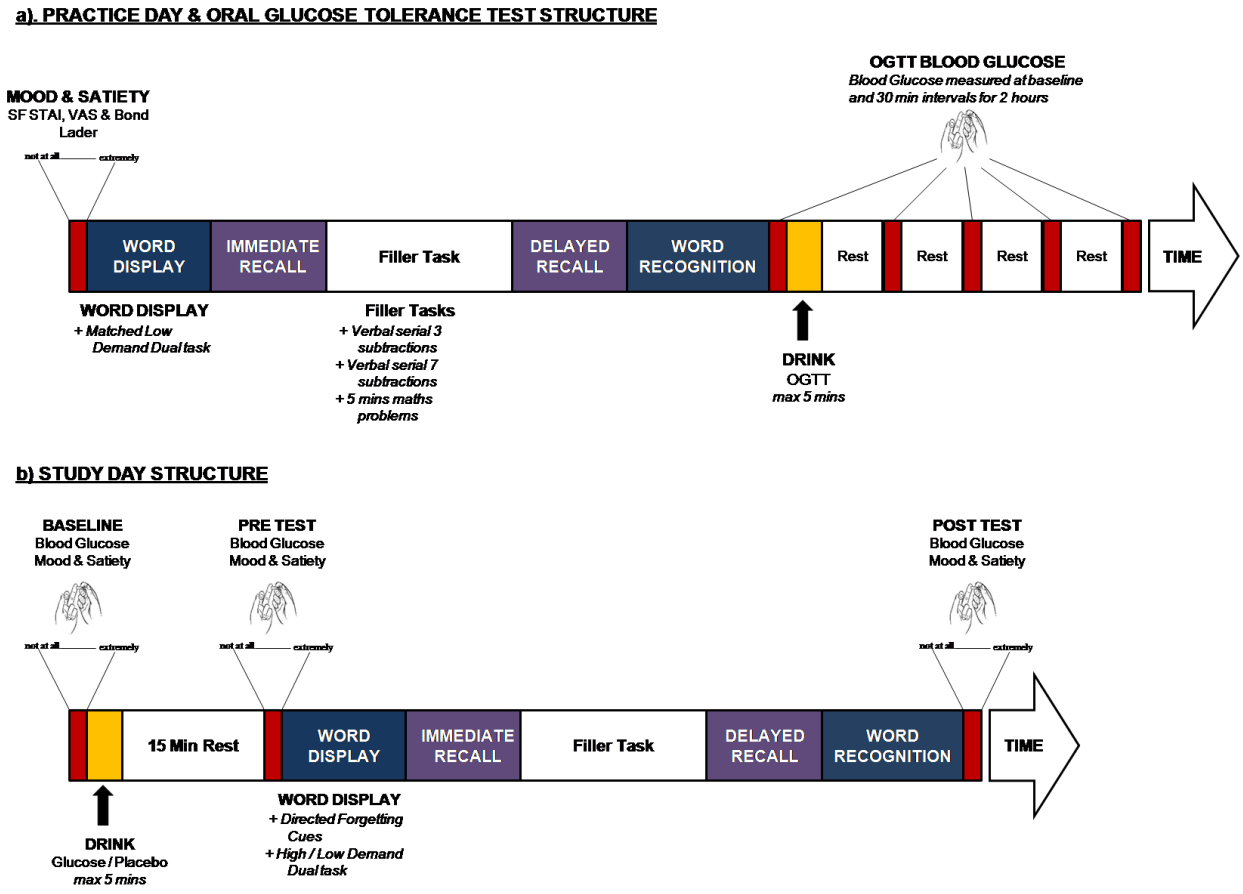


Figure 4.2 Schematics of the lab visits; *a) Practice and OGTT visit structure, and, b) Study day visit structure.*

On test visits, participants presented to the lab between 8am and 10am, following a minimum washout period of 48 hours from the OGTT. Baseline mood and satiety measures were taken prior to baseline blood glucose levels. Participants then consumed the drink and rested for 15 min to allow for absorption, followed by pre-test mood and satiety measures, then pre-test blood glucose. Participants were then briefed on the task that they would be undertaking, these instructions were reaffirmed by onscreen instructions and a demonstration of what was expected of them. Testing then commenced in the following order; 1) word display with high or low demand dual task (with remember/forget instructions presented after each stimuli), 2) immediate free recall for all presented items, 3) filler maths task, 4) delayed free recall for all items and 5) word recognition task. Post-test mood and satiety, then blood glucose levels were finally assessed (see figure 4.2b).

4.2.7 Statistics

A median split was utilised to group participants into better or poorer glucoregulators on the basis of their evoked glucose at 60 min minus baseline levels from the OGTT. A two-way (Glucoregulation x Time) ANOVA was conducted on OGTT data to assess glucoregulation differences between the two groups.

Blood glucose levels on study days were analysed via a 4 way mixed (Time x Treatment x Effort x Glucoregulation) ANOVA.

A four way mixed (Treatment x Effort x Response Type x Glucoregulation) ANOVA was used to analyse outcomes from the cued recall and word recognition tasks

Mood and satiety measures (Bond Lader, SF STAI & VAS) were analysed via a 4 way mixed (Time x Treatment x Effort x Glucoregulation) ANOVA on change from baseline scores. Prior to primary analysis, separate one way ANOVAs of baseline mood and satiety data were conducted to ascertain any baseline differences between groups. Where baseline differences were observed, baseline scores were entered as a covariate in an ANCOVA.

Where ANOVA revealed significant findings ($p<0.05$) post hoc pairwise comparisons with bonferroni correction applied were completed. Only the highest order interaction effects are reported in text. Lower effects are indicated in the outcome tables.

4.3 Results

4.3.1 Blood Glucose Levels

4.3.1.1 Oral Glucose Tolerance Test

Analysis showed no baseline differences in poorer and better glucoregulators' glucose levels prior to consumption of the glucose load. The OGTT response curve for all participants showed the normal pattern for a cohort of healthy young adults (see figure 4.3a). A two-way ANOVA revealed a time x glucoregulation interaction ($F(4,52)=18.170$, $p<0.0005$, $r=0.509$). Following post-hoc analyses poorer regulators (as grouped by the median split) were found to have significantly greater levels of circulating blood glucose levels than better regulators at; 30 min ($t(52)=3.279$, $p=0.002$), 60 min ($t(52)=7.586$, $p<0.0005$), 90 min ($t(52)=4.604$, $p<0.0005$) and 120 min ($t(52)=3.076$, $p=0.003$), see figure 4.3b.

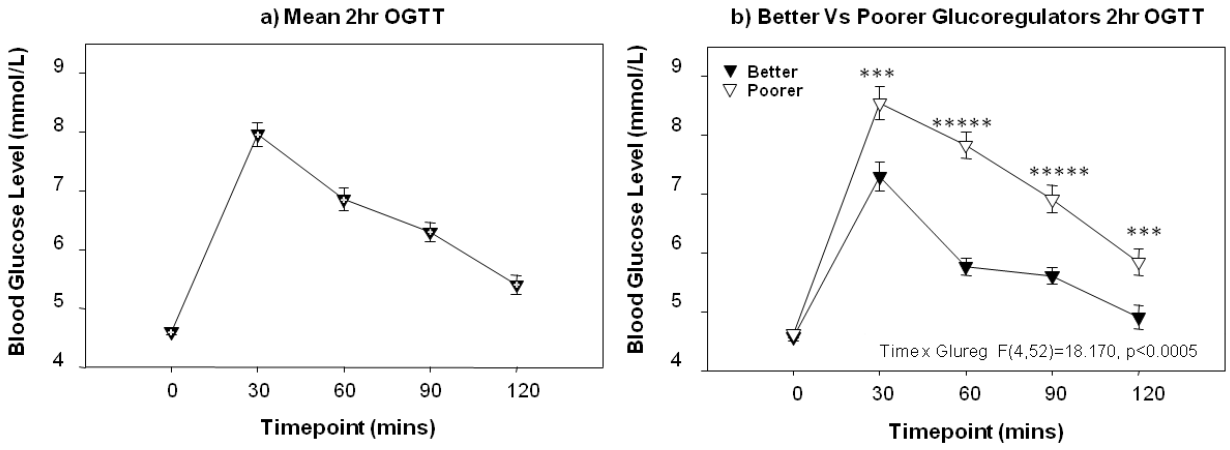


Figure 4.3 OGTT glucose levels; *a) Mean overall OGTT glucose levels, and b) Better vs. poorer glucoregulators OGTT glucose levels (***p<0.005, *****p<0.0005).*

4.3.1.2 Test Blood Glucose Levels

Table 4.1 below gives the means, SEM and significant effects for the test visit blood glucose levels.

Table 4.1 Means, SEM and significant effects for circulatory blood glucose levels. Significant effects and interactions are indicated in the final column *(Ti = time, Tr = treatment, *****p<0.0005).*

Outcome	Timepoint	Task Effort Level	Glucoregulation Group	Glucose				Placebo				Significant Effects & Interactions
				n=	Means	±	SEM	*n*=	Means	±	SEM	
Blood Glucose Levels	Baseline	High	Better	6	4.78	±	0.16	11	4.62	±	0.12	Ti ***** Ti x Tr *****
			Poorer	8	4.26	±	0.09	4	4.73	±	0.13	
		Low	Better	6	4.76	±	0.09	7	4.95	±	0.36	
			Poorer	9	4.80	±	0.13	8	4.49	±	0.15	
	Pre-Test	High	Better	6	6.79	±	0.55	11	4.52	±	0.14	
			Poorer	8	5.58	±	0.38	4	6.46	±	1.21	
		Low	Better	6	7.28	±	0.37	7	5.40	±	0.47	
			Poorer	9	6.87	±	0.36	8	4.53	±	0.11	
	Post-Test	High	Better	6	5.67	±	0.28	11	4.34	±	0.13	
			Poorer	8	5.27	±	0.24	4	5.46	±	0.60	
		Low	Better	6	5.56	±	0.62	7	4.48	±	0.25	
			Poorer	9	6.25	±	0.55	8	4.56	±	0.15	

Figure 4.4a below shows the mean glucose response curves for each treatment / effort condition.

A treatment x time interaction ($F(2,50)=16.831$, $p<0.0005$, $r=0.502$), revealed that a glucose drink increased circulatory glucose levels at pre-test ($t(50)=4.769$, $p<0.0005$) and post-test ($t(50)=3.680$, $p=0.001$).

No significant effects of glucoregulation were observed on circulatory blood glucose levels, although trends were apparent. These are not reported, although figure 4.4b illustrates some striking differences in treatment response by better and poorer glucoregulators. Specifically, the increased glucose levels observed in poorer regulators following placebo with high effort, which seem more in line with the changes seen for better regulators following glucose and high effort. Also surprising is the lower poorer regulators glucose levels following glucose with high effort than after placebo.

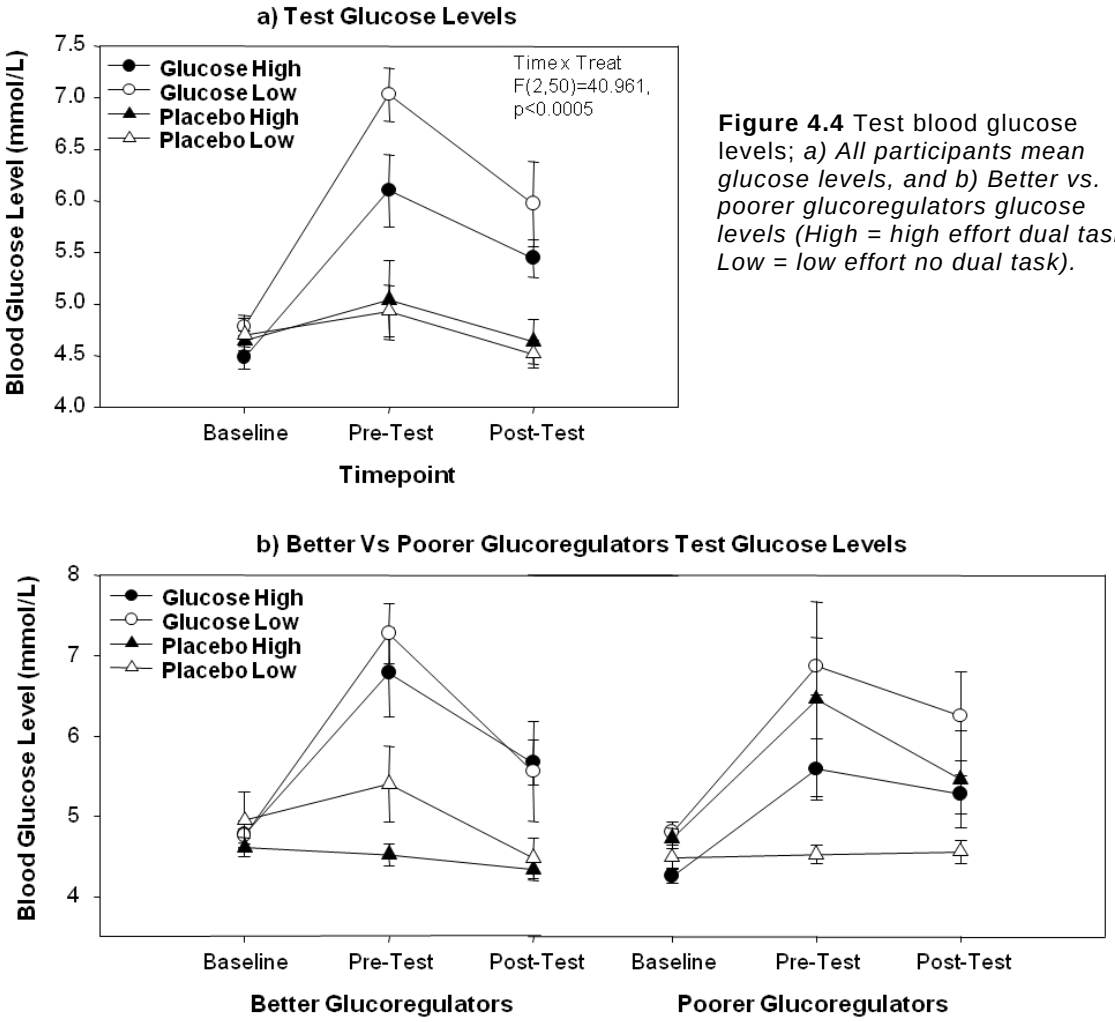


Figure 4.4 Test blood glucose levels; *a) All participants mean glucose levels, and b) Better vs. poorer glucoregulators glucose levels (High = high effort dual task, Low = low effort no dual task).*

4.3.2 Primary Task Outcomes

Table 4.2 below shows the means and SEM for the primary task outcomes. Any significant main effects and interactions for each outcome are indicated in the final column.

Table 4.2 Mean scores and SEM for each outcome from the primary tasks; word recall and recognition tasks. Significant effects and interactions are indicated in the final column *(Ef = Effort, Tr = Treatment, Glureg = Glucoregulation, Item= Initial item type [remember/forget or novel item], *p<0.05, **p<0.01, ***p<0.005, ****p<0.001, *****p<0.0005).*

Task	Outcome		Task Effort Level	Glucoregulation Group	Glucose				Placebo				Significant Effects & Interactions
					n=	Means	±	SEM	*n*=	Means	±	SEM	
Immediate Recall	#Errors		High	Better	6	3.33	±	0.71	11	1.45	±	0.31	Ef** Glureg* Ef x Tr* Glureg x Tr* Ef x Glureg**
				Poorer	9	1.22	±	0.22	4	0.75	±	0.48	
			Low	Better	6	0.83	±	0.48	7	0.71	±	0.18	
				Poorer	9	0.56	±	0.24	8	1.38	±	0.50	
	% Recalled	% Remember	High	Better	6	12.92	±	2.62	11	16.82	±	2.46	Ef***** Item***** Ef x Item***
				Poorer	9	15.28	±	1.97	4	22.50	±	1.44	
			Low	Better	6	25.00	±	3.16	7	30.71	±	5.28	
				Poorer	9	31.11	±	3.89	8	26.56	±	4.35	
		% Forget	High	Better	6	7.50	±	2.50	11	6.36	±	1.19	
				Poorer	9	7.22	±	1.69	4	7.50	±	1.44	
			Low	Better	6	8.33	±	2.47	7	8.57	±	2.83	
				Poorer	9	6.94	±	1.30	8	8.44	±	1.24	
Delayed Recall	#Errors		High	Better	6	1.67	±	0.67	11	1.64	±	0.47	
				Poorer	9	1.22	±	0.43	4	0.50	±	0.29	
			Low	Better	6	1.33	±	0.56	7	1.86	±	0.34	
				Poorer	9	0.89	±	0.39	8	1.75	±	0.62	
	% Recalled	% Remember	High	Better	6	8.33	±	2.79	11	13.64	±	2.03	Item***** Ef***** Tr* Item x Ef*
				Poorer	9	10.83	±	2.43	4	18.75	±	1.25	
			Low	Better	6	17.50	±	2.81	7	29.29	±	5.82	
				Poorer	9	23.89	±	3.98	8	23.44	±	3.50	
		% Forget	High	Better	6	5.83	±	2.39	11	5.00	±	1.17	
				Poorer	9	5.56	±	1.55	4	6.25	±	1.25	
			Low	Better	6	9.17	±	2.39	7	7.86	±	2.64	
				Poorer	9	6.94	±	1.66	8	9.06	±	2.83	
Word Recognition	% Correct	Remember	High	Better	6	55.00	±	6.06	11	54.55	±	4.64	Ef***** Item***** Item x Ef*
				Poorer	9	44.44	±	7.09	4	51.25	±	9.66	
			Low	Better	6	71.67	±	6.15	7	62.14	±	11.12	
				Poorer	9	70.00	±	8.82	8	70.63	±	4.86	
		Forget	High	Better	6	40.83	±	7.68	11	42.73	±	4.97	
				Poorer	9	42.78	±	6.35	4	52.50	±	12.99	
			Low	Better	6	51.67	±	5.11	7	40.71	±	5.82	
				Poorer	9	57.78	±	8.46	8	50.00	±	3.78	
		Novel	High	Better	6	81.67	±	3.18	11	73.91	±	4.83	
				Poorer	9	80.67	±	4.22	4	84.00	±	6.61	
			Low	Better	6	84.00	±	4.15	7	92.14	±	1.78	
				Poorer	9	85.89	±	3.45	8	88.88	±	2.65	
	Correct RT	Remember	High	Better	6	1146	±	88	11	924	±	83	Tr*
				Poorer	9	1227	±	127	4	824	±	77	
			Low	Better	6	979	±	42	7	850	±	74	
				Poorer	9	951	±	94	8	1062	±	125	
		Forget	High	Better	6	1054	±	100	11	936	±	60	
				Poorer	9	1134	±	91	4	881	±	74	
			Low	Better	6	1271	±	163	7	942	±	75	
				Poorer	9	991	±	78	8	1162	±	146	
		Novel	High	Better	6	1127	±	122	11	898	±	59	
				Poorer	9	1097	±	140	4	862	±	86	
			Low	Better	6	1056	±	108	7	862	±	82	
				Poorer	9	915	±	66	8	1020	±	65	
	Incorrect RT	Remember	High	Better	6	1172	±	109	10	1033	±	145	Item*
				Poorer	9	1203	±	140	4	1192	±	193	
			Low	Better	6	1112	±	84	7	1068	±	206	
				Poorer	7	1009	±	142	8	1101	±	106	
		Forget	High	Better	6	1154	±	152	10	930	±	88	
				Poorer	9	1070	±	157	4	1132	±	187	
			Low	Better	6	1263	±	284	7	889	±	84	
				Poorer	7	890	±	86	8	1229	±	99	
		Novel	High	Better	6	1503	±	193	10	1090	±	123	
				Poorer	9	1158	±	128	4	1031	±	101	
			Low	Better	6	1686	±	574	7	1426	±	294	
				Poorer	7	1114	±	107	8	1581	±	227	

4.3.2.1 Immediate Recall

Several interactions were found for the number of errors made during immediate recall. A treatment x effort interaction ($F(1,52)=7.081$, $p=0.010$, $r=0.346$), revealed that following glucose a greater number of errors were made in the high effort condition than following placebo ($t(52)=2.812$, $p=0.007$). Following glucose more errors were made in the high effort than low effort condition ($t(52)=3998$, $p<0.0005$), see figure 4.5a. A treatment x glucoregulation interaction ($F(1,52)=4.182$, $p=0.046$, $r=0.273$) revealed better regulators giving more errors following glucose than placebo ($t(52)=2.497$, $p=0016$), with better regulators also giving more errors than poorer regulators following glucose ($t(52)=3.016$, $p=0.004$), see figure 4.5b. An effort x glucoregulation interaction ($F(1,52)=7.781$, $p=0.007$, $r=0.361$), showed better regulators making more errors than poorer regulators in high effort ($t(52)=3.386$, $p<0.0005$), with better regulators making fewer errors following low than high effort ($t(52)=4.050$, $p<0.0005$), see figure 4.5 c.

Correctly recalled items gave an effort x item type interaction $F(1,52)=11.211$, $p=0.002$, $r=0.421$). Following both high effort ($t(52)=4.241$, $p<0.0005$) and low effort ($t(52)=9.404$, $p<0.0005$), more remember items were recalled than items designated as to be forgotten. High effort was also found to reduce recall of remember items ($t(52)=4.426$, $p<0.0005$) but not to effect to be forgotten items, see figure 4.5d.

4.3.2.2 Delayed Recall

A main effect of treatment revealed more of the items were recalled following placebo than glucose ($F(1,52)=5.223$, $p=0.026$, $r=0.302$).

At delayed recall, some evidence of forgetting was evident by slightly lower overall recall levels, although the pattern of item type recall remained the same as per immediate recall. An item type x effort interaction $F(1,52)=6.568$, $p=0.013$, $r=0.335$), showed greater recall of remember items in high effort ($t(52)=3.161$, $p=0.003$) and low effort ($t(52)=7.109$, $p<0.0005$). Again recall of remember items was greater following low than high effort ($t(52)=4186$, $p<0.0005$), see figure 4.5e.

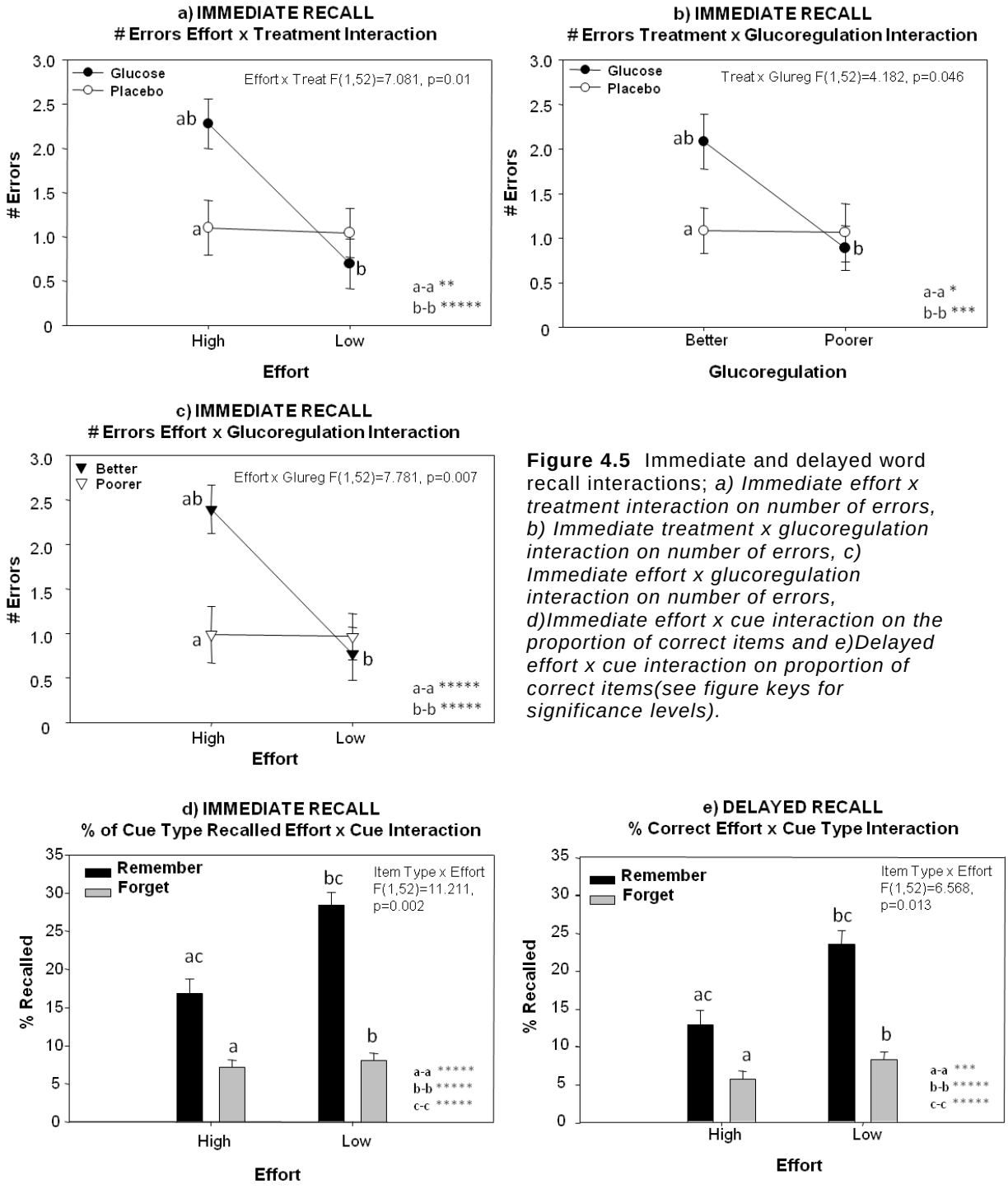


Figure 4.5 Immediate and delayed word recall interactions; *a) Immediate effort x treatment interaction on number of errors, b) Immediate treatment x glucoregulation interaction on number of errors, c) Immediate effort x glucoregulation interaction on number of errors, d)Immediate effort x cue interaction on the proportion of correct items and e)Delayed effort x cue interaction on proportion of correct items(see figure keys for significance levels).*

4.3.2.3 Word Recognition

A main effect of treatment (F(1,52)=5.361, p=0.025, r=0.274) showed correct recognitions were significantly slower following glucose than placebo.

A main effect of item type was observed for reaction times to give incorrect recognitions (F(2,48)=3.882, p=0.027, r=0.274), with remember items (t48)=2.512, p=0.046) and forget items (t(48)=2.808, p=0.021) responses both faster than for novel items, see figure 4.6a.

An effort x item type interaction on correct recognitions (F(2,52)=3.682, p=0.032, r=0.259) showed fewer remember items (t(52)=3.157, p=0.003) and fewer novel items (t(52)=2.524, p=0.015) correctly recognised following high effort. In the high effort condition, fewer remember items (t(52)=5.279, p<0.0005) and fewer forget items (t(52)=7.696, p<0.0005) were correctly identified than novel. In the low effort condition, again fewer correct recognitions of remember (t(52)=3.738, p=0.001) and forget (t(52)=7.696, p<0.0005) items were given compared to novel items. Additionally, significantly fewer forget items were recognised in comparison to remember items (t(52)=6.169, p<0.0005), see figure 4.6b.

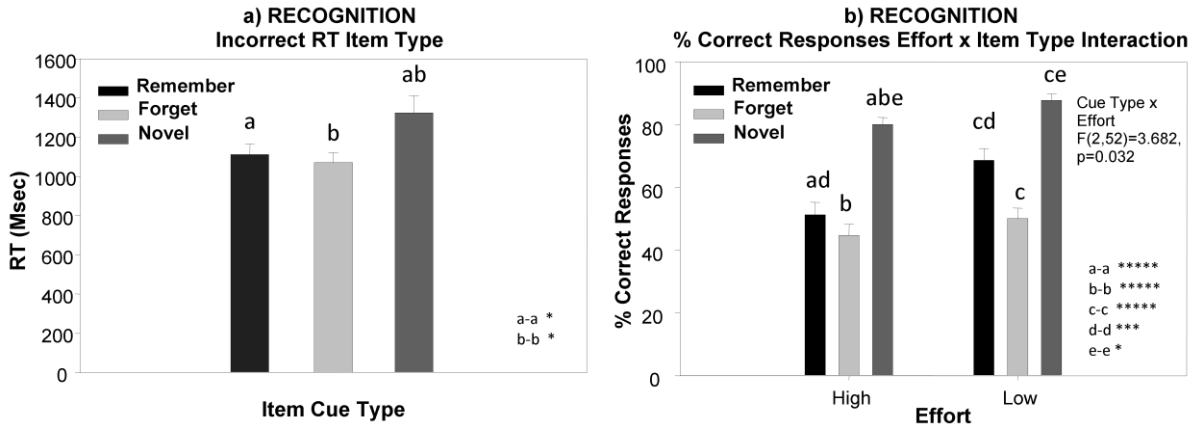


Figure 4.6 Word Recognition; *a) Main effect of Item type on incorrect RT and b) Effort x item type interaction on proportion of correct responses (see figure keys for significance levels).*

4.3.3 Secondary Outcomes: Mood and Satiety Measures

4.3.3.1 Baseline Scores

Prior to analysis of change from baseline data, baseline scores for all four conditions (2 x treatment and 2 x demand levels) for each outcome were subjected to a one-way ANOVA. Those receiving the glucose treatment reported significantly greater anxiety (via SF STAI) than placebo group (F(1,52)=29.951, p=0.019, r=0.605) at baseline. The high demand condition reported higher baseline hunger levels (F(1,52)=4.204, p=0.045, r=0.273) than low demand. For these outcomes, baseline measures were used as a covariate.

Table 4.3 Mean scores and SEM for each outcome from the secondary measures; Bond Lader, VAS and SF STAI. Significant effects and interactions are indicated in the final column *(Ti=Time, Tr = Treatment, *p<0.05, *****p<0.0005).*

Task	Outcome	Change	Task Effort Level	Glucoregulation Group	Glucose				Placebo				Significant Effects & Interactions
					n=	Means	±	SEM	*n*=	Means	±	SEM	
SF STAI	Stress	Baseline - Pre-Test	High	Better	6	-0.83	±	0.31	11	-0.55	±	0.43	-
				Poorer	9	-0.44	±	0.65	4	0.75	±	0.75	
			Low	Better	6	-0.33	±	0.42	7	0.14	±	0.86	
				Poorer	9	-0.44	±	0.38	8	-0.63	±	0.46	
		Baseline - Post-Test	High	Better	6	-0.33	±	0.56	11	0.45	±	0.97	
				Poorer	9	0.33	±	1.05	4	-0.75	±	0.25	
			Low	Better	6	0.17	±	0.48	7	0.00	±	0.98	
				Poorer	9	0.44	±	1.19	8	0.63	±	0.96	
VAS	Hunger	Baseline - Pre-Test	High	Better	6	-9.58	±	6.98	11	-2.50	±	2.80	-
				Poorer	9	-7.67	±	4.21	4	0.00	±	2.56	
			Low	Better	6	1.75	±	3.00	7	-5.93	±	3.71	
				Poorer	9	3.44	±	4.45	8	3.31	±	9.77	
		Baseline - Post-Test	High	Better	6	-6.08	±	8.58	11	1.91	±	3.05	
				Poorer	9	-2.44	±	5.78	4	3.25	±	2.68	
			Low	Better	6	6.67	±	10.72	7	3.21	±	5.18	
				Poorer	9	11.44	±	6.25	8	4.31	±	6.73	
	Thirst	Baseline - Pre-Test	High	Better	6	-18.50	±	10.57	11	-5.77	±	3.02	Ti * Ti x Tr *
				Poorer	9	-24.00	±	4.84	4	3.00	±	6.60	
			Low	Better	6	-15.42	±	10.01	7	-20.36	±	5.75	
				Poorer	9	-26.00	±	9.73	8	-16.31	±	6.90	
		Baseline - Post-Test	High	Better	6	-20.67	±	8.01	11	-4.45	±	5.89	
				Poorer	9	-12.44	±	8.49	4	3.63	±	11.09	
			Low	Better	6	-8.25	±	10.53	7	-22.29	±	7.57	
				Poorer	9	-1.67	±	5.46	8	-17.31	±	4.15	
	Alert	Baseline - Pre-Test	High	Better	6	10.75	±	5.57	11	3.73	±	4.05	-
				Poorer	9	12.72	±	6.68	4	10.25	±	8.34	
			Low	Better	6	3.17	±	5.47	7	18.86	±	6.94	
				Poorer	9	14.00	±	9.28	8	7.25	±	6.33	
		Baseline - Post-Test	High	Better	6	3.25	±	8.68	11	1.32	±	5.66	
				Poorer	9	16.83	±	8.29	4	12.25	±	7.32	
			Low	Better	6	-8.75	±	10.28	7	12.64	±	9.76	
				Poorer	9	9.00	±	11.47	8	8.31	±	9.32	
	Stressed	Baseline - Pre-Test	High	Better	6	-5.33	±	6.80	11	0.77	±	2.10	Ti *****
				Poorer	9	-0.89	±	5.56	4	-1.50	±	4.85	
			Low	Better	6	-7.67	±	4.76	7	-8.00	±	5.11	
				Poorer	9	-7.78	±	6.41	8	1.00	±	2.74	
		Baseline - Post-Test	High	Better	6	4.67	±	9.63	11	5.86	±	6.47	
				Poorer	9	13.22	±	8.57	4	4.00	±	7.70	
			Low	Better	6	-1.92	±	5.94	7	7.14	±	6.98	
				Poorer	9	6.67	±	6.61	8	12.44	±	10.88	
Bond	Alert	Baseline - Pre-Test	High	Better	6	7.19	±	2.61	11	1.68	±	3.44	-
				Poorer	9	10.98	±	2.60	4	1.19	±	3.63	
			Low	Better	6	1.91	±	2.57	7	6.08	±	3.74	
				Poorer	9	5.56	±	2.67	8	12.63	±	4.57	
		Baseline - Post-Test	High	Better	6	5.04	±	5.07	11	5.66	±	3.30	
				Poorer	9	9.47	±	5.45	4	2.97	±	2.75	
			Low	Better	6	3.67	±	5.98	7	13.70	±	4.05	
				Poorer	9	1.56	±	4.85	8	6.49	±	11.25	
	Content	Baseline - Pre-Test	High	Better	6	6.83	±	1.49	11	-0.25	±	1.77	-
				Poorer	9	6.58	±	3.13	4	0.15	±	1.25	
			Low	Better	6	2.50	±	1.19	7	1.77	±	2.89	
				Poorer	9	6.09	±	5.37	8	5.20	±	3.59	
		Baseline - Post-Test	High	Better	6	4.73	±	4.17	11	-3.20	±	2.14	
				Poorer	9	5.04	±	4.48	4	-1.20	±	0.80	
			Low	Better	6	6.50	±	2.85	7	0.26	±	3.14	
				Poorer	9	-1.93	±	6.03	8	-5.70	±	9.15	
	Calm	Baseline - Pre-Test	High	Better	6	1.75	±	2.02	11	-1.82	±	1.66	Ti *****
				Poorer	9	-1.78	±	3.95	4	-0.88	±	2.11	
			Low	Better	6	9.25	±	3.99	7	1.00	±	5.08	
				Poorer	9	5.33	±	8.53	8	-2.63	±	6.06	
		Baseline - Post-Test	High	Better	6	-8.17	±	7.20	11	-7.18	±	3.86	
				Poorer	9	-10.67	±	5.67	4	-0.88	±	2.75	
			Low	Better	6	-12.00	±	5.32	7	-9.00	±	6.67	
				Poorer	9	-2.83	±	10.45	8	-20.81	±	11.32	

4.3.3.2 SF STAI

No significant effects were found for this measure.

4.3.3.3 VAS

Levels of 'Stress' as measured by VAS showed a significant time effect; (F(1,52)=16.496, p<0.0005, r=0.491), with increased reported stress at post test.

No effects of 'Hunger' were observed. A treatment x time interaction (F(1,52)=4.475, p=0.039, r=0.281) on reported 'Thirst', was evident at pre-test, thirst was decreased further by a glucose drink than placebo (t(52)=2.079, p=0.043). Following the glucose drink, thirst increased significantly by post test (t(52)=2.990, p=0.004), see figure 4.7.

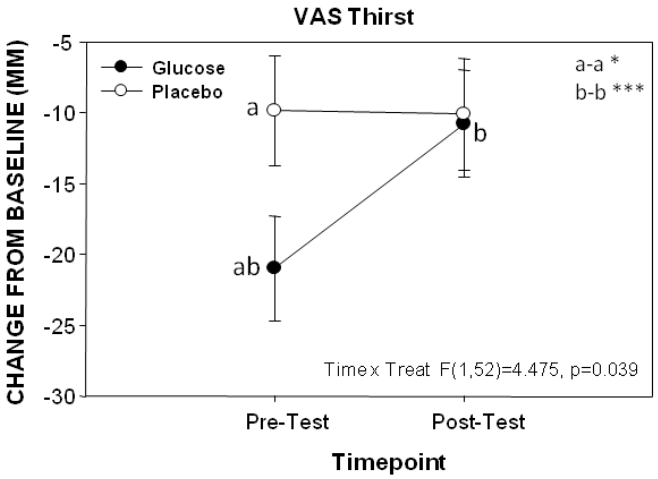


Figure 4.7 VAS Thirst time *x treatment interaction (see figure key for significance levels).*

4.3.3.4 Bond Lader

A main effect of time indicated decreased levels of calm at post test (F(1,52)=16.488, p<0.0005, r=0.491).

4.4 Discussion

4.4.1 Summary of Main Findings

This chapter aimed to investigate whether the glucose facilitation effect on memory is preferentially targeting encoding processes and also how these differ between better and poorer glucoregulators. The DF effect was evident, with increased recall of TBR items compared to TBF items. Administration of a glucose drink did not increase the magnitude of this effect, which suggests that glucose is not increasing encoding efficiency. The high effort manipulation reduced the recall of TBR items, but not TBF items, which suggests that the increase in effort is limiting elaborate encoding without influencing effective cessation of TBF items. Some interesting findings were revealed with regards to the number of errors that were made during the recall phase, with better glucoregulators making more errors following high effort and also having consumed the glucose drink (although no three way interaction was found). This is discussed in terms of better glucoregulators attempting to retrieve unconsolidated items.

4.4.2 Blood Glucose

Glucoregulation median splits formed two groups of regulators, whose response to the OGTT differed significantly, with the higher circulatory blood glucose levels at 30, 60, 90 and 120 min post ingestion for poorer regulators. This suggests that this grouping does allow interpretation of the findings to be discussed in terms of assessing the performance of 2 cohorts representing better and poorer levels of glucoregulation. Fasting blood glucose levels did not differ between the cohorts, and presented within normal fasting range. A treatment x time interaction on blood glucose on test visits confirmed that a glucose drink successfully elevated circulatory blood glucose throughout the test visit.

Whilst no significant glucoregulatory effects on test visit blood glucose levels were found, trends (not reported) do hint at a possibility that glucoregulation may be impacting on blood glucose. Visual representations of the blood glucose levels for better versus worse poorer regulators also seem to suggest that responses to effort and treatment manipulations were different between the 2 levels of glucoregulators, see figure 4.4b. Caution is advised when interpreting the glucoregulatory effects presented here as poorer glucoregulators receiving the placebo treatment with the high dual demand task, (due to

the randomised nature of the treatment allocation and the median split) resulted in a sample size of 4, which is likely to have underpowered the glucoregulation analysis.

4.4.3 Primary Outcomes

4.4.3.1 Word Recall: Immediate and Delayed

The primary outcomes of this chapter are the word recall scores. DF is displayed by fewer TBF items, being recalled in comparison to TBR items. The paradigm successfully induced DF, with greater recall of TBR items than TBF at both immediate and delayed recall. The highly demanding dual task successfully induced a performance deficit, with reduced overall recall at both time points as predicted. Consequently this manipulation did create an environment in which performance was below ceiling levels and with a greater potential for treatment effects to become apparent. The decreased recall following the high demand dual task was not uniform across cue types, with no significant decrease in TBF items recalled, but significantly fewer TBR item recalled. This finding suggests that the high effort dual task decreased encoding ability for the TBR items, but that the processed involved in TBF were unaffected. This lends considerable evidence to the literature that suggests that the item method of directed forgetting is primarily targeting encoding processes and not retrieval inhibition.

The effects on accuracy were not straightforward. As no treatment effects were found on correct immediate recall, it would seem that a glucose load did not act to improve (or impair) encoding processes. At delayed recall fewer items were correctly recalled following glucose than placebo, although no treatment effects were found in relation to item cue type (TBF/TBR) recall. This may indicate some detrimental effects in recall performance following a glucose load.

Whilst the number of error responses given at delayed recall did not yield any significant effects, those given at immediate recall did. Following glucose with the high demand task, more errors were produced during immediate recall. Better regulators given glucose and better regulators following the high demand task, also generated more errors than the other groups. No treatment differences in errors generated were found following low effort, for placebo or for poorer regulators. It is unclear as to why these groups produced (approximately 100 – 150%) more error items. Possibly due the between subjects design, these findings may result from this particular sub group of the participants being more

prone to producing errors, however, as they did not display these same effects at delayed recall, this seems unlikely (additionally the data were checked to ensure that individual datum were not skewing the finding). It is possible that better regulators are attempting to retrieve items that were designated as to be forgotten, but are unable to successfully do so due to improved encoding efficiency and cessation of processing of the TBF items. Equally they may be attempting to remember TBR items that were not elaborately encoded due to the high dual demand task. These increased errors may hint at potential enhancements by glucose in the high demand task and also better regulators advantageous encoding. Such an interpretation is speculative at this point and warrants further investigation.

There was a main effect of treatment at delayed recall. A greater overall proportion of the original items were recalled following consumption of placebo than glucose. This suggests (that at least in this particular task or for this specific cohort), raised circulating glucose levels did not facilitate overall delayed recall on this task, but actually impaired performance. Glucose treatment actually lead to decreased overall delayed recall, but did not selectively decrease recall of forget items, which would have indicated a glucose facilitation via improved encoding efficiency. No such interaction was found with treatment and glucoregulation, which does not support the prediction that poorer regulators may benefit from improved encoding efficiency with raised blood glucose levels. However, as previously mentioned, such an interpretation may be undermined by low power.

4.4.3.2 Word Recognition

At recognition, the distribution of item type correct recognitions followed that of the recall task, with more TBR items recognised than TBF, and an effort x item type interaction. In both dual task effort levels, the novel items were the most accurately identified, more so following low than high effort. Also following the recall results, the TBF items across effort manipulations were similarly recognised, at levels lower than the 50% chance recognition. This was not the case for the TBR items where the recognition rate following the high demand task was not significantly higher than TBF and was around chance levels (51%).

The recognition rates of TBR in the high demand and low demand tasks are comparable to those seen in chapter 3 for the R/K/G recognition outcome, which suggests that recognition (and in turn encoding and retrieval processes) for TBR items in this study are

consistent with those in which all presented items are to be remembered. The similar recognition for TBR and TBF following the high demand task suggest that the high demand task in chapter 3 was interrupting encoding processes, and as such it may be that the protective glucose effects seen there are a result of glucose improving encoding efficiency. No such glucose protective effects were seen for recognition in this study, suggesting that the finding in chapter 2 is not robust across all types of memory processing, or that the effects in this chapter were present but with effect sizes too small to reach significance.

4.4.4 Secondary Outcomes: Mood & Satiety

Very few of the mood and satiety measures yielded significant findings, with no effort or glucoregulatory effects observed at all. Participants did report increased stress (via VAS) and decreased calm (via Bond Lader) at post test, however, this was not differentially affected by dual task demand manipulations. This suggests that completing the study in itself elicited increased subjective feelings of stress and concomitantly decreased calm, this effect was not increased by the imposition of a greater or lesser demanding dual task. It should be noted that whilst this was a between participants design, the practice visit was very similar to the test visit for the low demand dual task, with the exception of the remember/forget cues at word display. As such participants were familiar with the lab environment and the type of tasks they were asked to complete. As post test mood measures were completed approximately 25 min after the word display with dual task, it may be that any differences in stress experienced between the high and low effort groups, had subsided by post test measurements and so was not detectable in this measurement.

Whilst both treatments decreased thirst at both pre and post test, thirst was reduced substantially more by glucose than placebo at pre test, with the effect having abated by post test. It is possible that the glucose drink was more thirst quenching than the placebo. Evidence is available to suggest that drinks containing glucose may be more effective at restoring hydration status than comparable drinks without glucose (Evans et al., 2009), which may account for this finding.

4.4.5 Limitations

Unfortunately smokers were not excluded and due to the random allocation to condition, by chance all seven of the smokers were placed in the glucose condition (4 low effort, 3 high effort), five were classified as poorer regulators by the median split. Smoking has been associated with increased incidence of impaired fasting glucose (Houston et al., 2006, Park et al., 2008, Rafalson et al., 2009). Potentially this may have contributed to the lack of treatment effects observed in this chapter. To eliminate this potential confounding factor, smokers will be excluded from future studies.

It is possible that although two different glucoregulatory cohorts were identified, the poorer regulators were not impaired to a sufficient level to allow differential facilitation by a glucose load, or that such a treatment effect was present but failed to reach a large enough effect size to be detected in this relatively small sample. This may account for the lack of treatment effects observed throughout the memory tasks presented in this chapter. This possibility could be evaluated using similar methodology as employed in this chapter, to test the effects of glucose administration in older adults. This population has previously been shown to display deficits in memory encoding in older adults through decreased DF (Dulaney et al., 2004, Sego et al., 2006, Zacks et al., 1996). This population also display declining levels of glucoregulatory control (Awad et al., 2004, Messier et al., 1999) and subsequently may be more susceptible any glucose facilitation effects on this paradigm.

4.4.6 Conclusion

Whilst the general consensus within the DF literature is that encoding efficiency is the most likely and most influential aspect of memory in generating DF in the item method, it has also been suggested that retrieval inhibition underlies the decreased recall of TBF items. The evidence presented here seems to support the view that DF results from curtailment of encoding following the TBF cue onset. During the high demand dual task, the recall of TBR items was reduced whilst resources at encoding were divided. The recognition task further supports this, with higher recognition rates than recall (as per normal). However, should retrieval inhibition be the main influencing factor, we would have expected the inhibition to be released upon display of the TBF items. Recognition rates for the TBF failed to increase above chance levels, suggesting that the items were not being released from retrieval inhibition.

A glucose load did not facilitate recall or recognition performance, with placebo eliciting greater overall recall at delayed recall. There were more error recall responses following glucose at immediate delay but not at delayed recall. The reasons for this finding are unclear, but as the increased error rates were more prominent following high demand and in better regulators, this tentatively suggests that rather than an impairment, this finding may represent increased attempts to (admittedly incorrectly) retrieve TBR items that were not fully encoded during the display phase. Should this finding be robust, it may represent a performance advantage following glucose in better regulators. This could be further investigated by utilising a range of secondary tasks differing in difficulty and examining how this impacts on both error rates and TBF / TBR item recall.

From the findings in this chapter it is not possible to definitively state that poorer and better regulators encoding efficiency capabilities differ. The high effort dual demand task did not increase the magnitude of directed forgetting displayed, but instead limited the recall of TBR items whilst having no real impact on TBF items. Some evidence is presented suggesting that glucose may be facilitating better regulators following the high demand dual task, although this is presented in the form of increased errors, but not at the expense of decreased correct recalls. No evidence was found to suggest poorer regulators benefitted from glucose administration in this task.

CHAPTER 5. AN INVESTIGATION OF GLUCOREGULATORY AND GLUCOSE FACILITATION EFFECTS ON INHIBITION THROUGH RETRIEVAL INDUCED FORGETTING

5.1 Introduction

Chapter 4 addressed the issue of whether glucose and glucoregulation had an impact on encoding efficiency. More specifically the ability to effectively cease the encoding of irrelevant information (or potentially increase the inhibition) from further cognitive processing was investigated. As per chapter 3, the findings were not definitive. Glucose was not found to increase encoding efficiency through increased directed forgetting. However, a more subtle finding of increased errors during immediate recall may hint at potential enhancements by glucose in the high demand task and also that better glucoregulators may display advantageous encoding. These errors may represent a retrieval advantage of more tenacious attempts to retrieve inhibited items that may not have been elaborately encoded (TBF items or TBR following high effort). The findings from chapter 4 suggest that while better regulators appear to have superior early cognitive control of presented information and encoding, it remains unclear as to whether this control primarily targets encoding or inhibition of such items. By utilising alternative paradigms this issue may be (at least to some extent) resolved, with greater insight gained.

This chapter utilises a closely related paradigm, referred to in the literature as Retrieval Induced Forgetting (RIF). Unlike the directed forgetting paradigm in chapter 4, RIF induces forgetting through repeated retrieval and hence practice of semantically related items. This repeated retrieval results in subsequent inhibition of non practised items. Such forgetting induced via inhibition is of key importance to an individual's day to day functioning. This adaptive forgetting limits the impact of outdated or intrusive memories, which may negatively impact upon performance (Anderson, 2003, Anderson and Bell, 2001, Anderson and Green, 2001).

The RIF paradigm was developed by Anderson, Bjork and Bjork (1994), and has been used extensively over the last 15 years. The paradigm results in robust facilitation of recall for practised items and suppression of retrieval for semantically related items (Levy and Anderson, 2002, Anderson et al., 2000, Anderson, 2003, Groome and Sterkaj, 2010).

In the typical RIF experiment, participants study lists of high taxonomic category–exemplar pairs (e.g., fruit—orange, drinks—scotch, fruit—banana). Retrieval practice on half of the exemplars from half of the categories by completing cued stem recall tests (e.g., fruit-or_____) is then completed. Each practiced item is cued three times during the retrieval practice phase to increase the magnitude of the effect on related items. After a retention interval, participants are given a final cued recall test for all the exemplars. Performance on this test can be measured for the recall of the three item types: repeatedly practised/retrieved items (Rp+), unpractised items from the practiced taxonomic categories (Rp-), and unpractised items from unpractised categories (NRp) which are not subjected to retrieval interference.

Using this paradigm, recall for the unpractised items from repeatedly cued categories (Rp-) are recalled less than the items from unpractised categories (NRp). The repeated retrieval of selected category-item exemplars, causes forgetting of semantically related category items that are not repeatedly cued and retrieved. Further, the increased recall of repeated cued items is generally higher than that of unpractised categories, providing evidence of increased activation and availability via the repeated cuing.

Although there is some debate as to the mechanisms that are employed in this paradigm, the general consensus is that it is an inhibition mechanism, the function of which is to suppress interference from competing items in memory (for a review see Anderson, 2003). An EEG study (Johansson et al., 2007) also support the inhibition approach with prefrontal event related potentials (ERPs) elicited during the practice phase (where inhibition is thought to be occurring), being predictive of later RIF.

The implications of this inhibition mechanism for everyday functioning are related to the possibility that RIF may assist in the selective retrieval of a required memory by inhibiting competing memories (Anderson and Neely, 1996). Groome and Grant (2005) found evidence that individuals showing a weak RIF response to the paradigm also reported more everyday memory failures. It has also been suggested that individuals with weak RIF are more vulnerable to intrusive memories (Groome et al., 2008), as these are not inhibited upon retrieval of a rival memory. Groome further suggests that this may increase an individual's susceptibility to depression, a feature of which is a tendency to experiences unwanted intrusive thoughts (Groome and Sterkaj, 2010), with reduced RIF also found in negative mood states (Bauml and Kuhbandner, 2007).

Although nutritional interventions have not been investigated in conjunction with this paradigm, several studies involving pharmacological interventions and clinical groups

have recently been published (scopolamine & nicotine: Edginton and Rusted, 2003, depression: Groome and Sterkaj, 2010, nicotine: Rusted and Alvares, 2008). Previous successful pharmacological interventions have assessed the potential cholinergic effects of nicotine and scopolamine on RIF (Edginton and Rusted, 2003, Rusted and Alvares, 2008). Nicotine (a cholinergic agonist) led to increased inhibition of Rp- items, but did not affect recall of Rp+ items (Edginton & Rusted 2003). One of the suggested mechanisms of glucose facilitation on memory is via the increased ability for acetylcholine synthesis in the brain, since the breakdown of glucose involves the generation of the cholinergic precursor, acetyl Coenzyme A (Messier, 2004). Should glucose administration elicit a similar response, support for this mechanism of glucose facilitation may be drawn (although such an effect does not preclude an effect of glucose via increasing metabolic activity). Such studies, in conjunction with the evaluation of glucoregulatory control and potential glucose facilitation presented in this chapter, may add considerable insight into the understanding of the underlying mechanisms of this paradigm on memory. Additionally knowledge of the mechanisms by which glucoregulation and glucose loads may be interacting with episodic memory and inhibitory processes may also be further disentangled.

This chapter aims to investigate whether the potentially facilitating effects of glucose are preferentially targeting inhibition processes, and whether impairments in inhibition may be a resultant feature of poor glucoregulatory control. Several hypotheses were tested in this study:

- That better glucoregulators will display greater inhibitory responses than poorer regulators. Evidence of this may present as fewer unpractised items from the practiced categories (Rp-) recalled during delayed recall. This finding would support the proposal that there are decrements in inhibitory processes in poorer glucoregulators.

- Slower or fewer rejections of Rp- items by poorer glucoregulators during word-pair recognition would also suggest decreased inhibitory processes. As inhibition is believed to be 'released' via exposure to an actual item, any evidence from the recognition task is likely to show a smaller effect if detectable.

- The high demand dual task is expected to decrease overall recall. Practically it is not plausible to impose a dual task during the repeated retrieval phase of RIF, however, as the repeated cuing is completed immediately following the high effort word display, carryover effects from the increased effort may still exert an

influence during the repeated cuing phase. Increased demand may induce deficits in inhibition of the Rp- items in better and poorer regulators, which may be facilitated back to normative levels (or protected from decrements) following a glucose load. Such a finding would provide evidence that glucose may be influential in mediating facilitation of inhibition processes under circumstances when suboptimal performance is induced.

5.2 Materials and Method

5.2.1 Design

A placebo-controlled, double blind, randomised, crossover design was used in which various cognitive and mood/appetite outcomes were assessed (see below). The independent variables were treatment (25 g glucose or placebo) and effort (high demand dual hand movement task or low demand no dual task). Glucoregulation was assessed using an Oral Glucose Tolerance Test (OGTT) and a median split used to allocate participants to better or poorer glucoregulation groups.

5.2.2 Participants

Twenty-two self reported healthy volunteers (11 males, mean age 24.00 yrs, *SD 4.12*) took part in this study which was approved by the Northumbria University Division of Psychology Ethics Committee. Following completion of the study participants received an honorarium of £80. Prior to participation, informed consent and screening were completed, ensuring all participants were in good health, free from illicit and recreational drugs including prescription and 'over-the-counter' medications (excluding contraceptives), did not suffer from any metabolic disorders such as glucose intolerance or diabetes, or any allergies that would prevent consumption of the treatments. All participants were non smokers. Demographic and morphometric information recorded including years in education (mean 16.55 yrs, *SD 2.09*), BMI (mean 24.42, *SD 6.82*) and WHR (mean 0.84, *SD 0.05*), see appendix 1.4 for full individual participant characteristics. Prior to each lab visit, participants fasted for a minimum of 12 hours, drinking only water over this period. Food diaries were kept for the 24 hours prior to all visits to aid fasting compliance, see appendix 3.2.

5.2.3 Blood Glucose Levels

Blood glucose levels were monitored using an Accutrend Plus diagnostic instrument and Accutrend Glucose test sticks (Roche Diagnostics, Germany). Blood glucose levels were measured via capillary finger prick at baseline, pre-test (15 min post dose) and at post test (~55 min post dose) for test visits. Measurements were also taken at these points over

the practice session although no treatment was administered. Following completion of the practice session an OGTT was completed with glucose levels measured at Baseline, 30, 60, 90 & 120 min post glucose load.

5.2.4 Treatments

The glucose load for the OGTT was comprised of 75 g glucose in 250ml of water. Test treatments comprised of 25 g glucose (active) or saccharine (placebo), with 20ml Robinsons no added sugar orange cordial, made up to a volume of 200ml with water. Participants were permitted up to 5 minutes in which to consume the drink, with the end of the drink consumption time locked as 0 mins (t=0). Study day treatments were prepared by a disinterested third party in order to ensure the study remained double blind. Drinks were made the evening prior to the participants visit and were kept refrigerated overnight in sealed containers.

5.2.5 Assessment

5.2.5.1 Appetitive and Mood Scales

At baseline, 15 min post dose (pre-test) and completion of test battery (post test, approx 55 min), computerised appetitive and mood scales were completed. Participants rated 'hungry', 'thirsty', 'alert' and 'stressed' levels on a 100 mm visual analogue scale (VAS), by moving an on screen slider to the appropriate position on the scale labelled 'not at all' and 'extremely', on the left and right ends respectively, to indicate their current state for each descriptor. A computerised version of the Bond Lader (Bond and Lader, 1974) was also completed along with the paper Short Form State Trait Anxiety Inventory (SF STAI) (Tluczek et al., 2009, Marteau and Bekker, 1992). Additionally at post test, a paper VAS for 'effortfulness' of the visit was completed.

5.2.5.2 Retrieval Induced Forgetting

The RIF paradigm was based on the original as devised and reported by Anderson et al. (1994), although some modifications were made in order to utilise a repeated measures

design. Twenty-four category item exemplars were presented on the centre of a screen for 5 seconds, with an inter-stimulus delay of 1 second, in line with the published RIF literature. Category labels were presented in capitals, with only the first letter of the category items capitalised, see figure 5.1a.

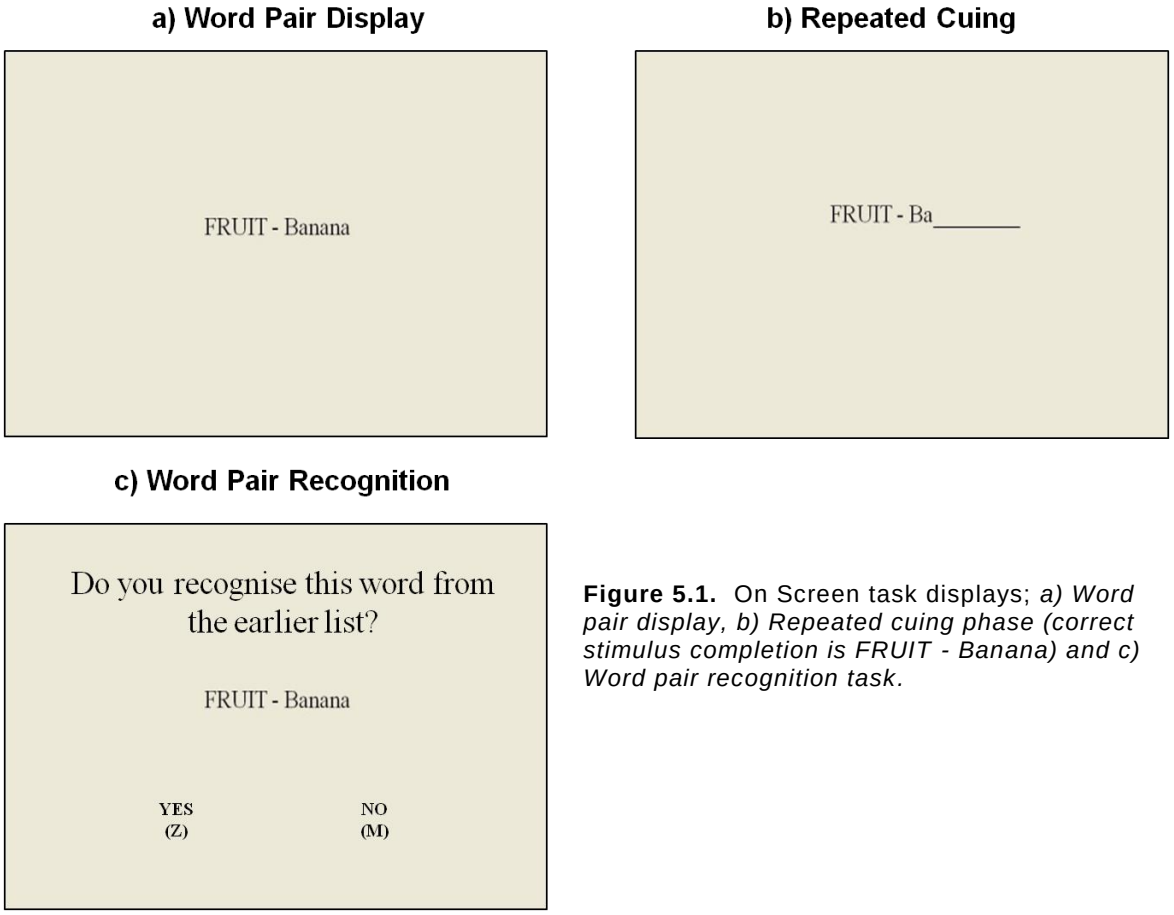


Figure 5.1. On Screen task displays; *a) Word pair display, b) Repeated cuing phase (correct stimulus completion is FRUIT - Banana) and c) Word pair recognition task.*

Separate lists were generated for each of the 5 visits (1 practice and 4 study visits). Each visit list comprised of 4 categories, with 6 category–item exemplars displayed per category. Presentation was randomised such that no 2 items from the same category were presented sequentially, with category group cycled so as the first, second, third etc items from each category were displayed before moving onto the next item. This method of randomization was also applied to the repeated cuing phase, whereby half of the items from half of the categories were repeatedly cued and retrieved.

The categories and category items were selected from Van Overschelde et al. (2004) Category Norms: An Updated and Expanded Version of Battig & Montague (1969) Norms, with categories pertaining to biased Americanised categories excluded along with categories with fewer than 12 individual items. From the selected categories, 6 items from the 12 most frequently generated for that category (every other item of the top 12 in the

frequency list) were selected to be used as target Category-item exemplars, with the remaining 6 items to be employed in addition to the targets during a word pair recognition task.

From the 24 categories, 12 were randomly selected and designated to the repeated practice categories. From these categories, 3 of the 6 target items were randomly selected to be repeatedly cued (becoming Rp+ items) and the 3 remaining not to be repeatedly practiced and recalled (Rp- items). All items from the unpracticed categories are designated as NRp items. Repeatedly cued and practiced items appeared on screen as the category with a two letter stem, see figure 5.1b. Participants were issued with an answer booklet in which they wrote down the item from the word display which would complete the stem. Each repeatedly cued category-word stem was presented to the participant three times, ordered as described above, and remaining on screen for 8 seconds, with an inter stimulus delay of 1 seconds. A total of 18 cues were displayed (3 items from 2 categories, each cued 3 times).

5.2.5.3 Category Cued Recall

Participants were presented with on screen instructions requiring them, for each of the four categories in turn, to recall as many of the items from the specified category that were previously displayed, and write them down on the paper supplied. Participants were given 30 seconds per category. The order of the category recall was linked to the visit number, with each study visit utilising one of the four possible orders of 2 cued x 2 non cued categories (e.g. visit 3; 1st cued category, 2nd non cued category, 3rd, non cued category and 4th cued category).

5.2.5.4 Word Recognition

Forty-eight word pairs were presented serially consisting of the 24 original target pairs, and 24 additional items comprised of the same 4 categories as per the initial display, but with a further 6 novel category items. Word pairs were displayed in the centre of the screen, above which the question *'Do you recognise this word pair as one that was shown earlier?'.* Participants were required to respond as quickly and accurately as possible via 'Z' key press for a recognition or 'M' key press for non recognition, by the appropriate index finger, see figure 5.1c.

5.2.5.5 Dual Hand Movement Task

A dual task was used to incite a performance deficit in individuals who otherwise may be performing at ceiling levels. This creates an opportunity for any facilitation by glucose or glucoregulatory effects to become apparent. Due to the nature of this paradigm it is necessary to use a non-visual dual task, as this modality is engaged solely in the word display element in line with previous research utilising this paradigm. As such a continuous hand movement task which has previously successfully been employed in chapter 3 and previous literature (Foster et al., 1998, Sünram-Lea et al., 2001) was also enlisted here. Participants completed complex hand movement sequences, whilst simultaneously attending to the on screen word display. Two sequences of movements were completed; sequence 1: Fist – Chop – Slap and sequence 2: Back Slap – Chop – Fist. One sequence of hand movements was completed for each word pair displayed. Four repetitions of each sequence were made before switching to the alternate sequence on every fifth word pair presentation. This switching between sequences ensures hand movements are monitored and does not become autonomous. Please see figure 3.2 for a photographic illustration.

Participants were advised to complete both tasks to the best of their abilities, with no advice given to prioritise one task over the other. To ensure compliance with the hand movement task, video cameras recorded movements throughout the task and these were checked. This element of the task was briefly rehearsed during the practice visit, with written reminder sheets being issued to participants during the dose absorption period on occasions when they were required to complete the dual task.

5.2.5.6 Retention Period Tasks

Chapter 3 and 4 both utilised a pencil-and-paper maths task (long multiplication) during the 10 minute filled retention period. Whilst this had been seemingly effective in preventing rehearsal, this task was observed to create (anecdotally from participants) increased stress and anxiety. Participants expressed dismay at being asked to undertake the task, which in most cases had not been undertaken for several years, resulting in a subsection of participants 'giving up' and failing to fully interact with this task. Subsequently this study employed a series of shorter tasks (serial 3 subtractions, serial 7 subtractions and Rapid Visual Information Processing [RVIP]), in order that engagement with the tasks for the full duration could be assessed.

5.2.5.6.1 Serial Sevens & Threes Subtractions

The task was originally designed by Hayman (1942), and is sensitive to both lowered (Taylor and Rachman, 1987) and raised (Kennedy and Scholey, 2000, Scholey et al., 2001) blood glucose levels. This study utilised a computerised version of the serial subtraction tasks. Participants counted down from a random starting number (between 800 and 999). The starting number appeared in the centre of the screen and disappeared following the input of the first response. Responses were entered using the linear number keys, with asterisks appearing onscreen in place of the actual digits. Once the 3 digit response had been input, pressing 'Enter' submitted and cleared the response from the screen. Participants could use the 'Backspace' key to delete errors. In the case of an error participants were instructed to continue subtracting from the last number entered, with subsequent responses scored in relation to that response. Participants first completed the serial threes subtraction task for 2 minutes in which they continually subtracted threes, followed immediately by serial seven subtractions for a further 2 minutes (standardized instruction screens appeared prior to threes and sevens subtraction tasks).

5.2.5.6.3 RVIP

This task has been has been shown to be sensitive to raised blood glucose levels (Donohoe and Benton, 1999b). A continuous series of rapidly changing digits appear in the centre of the screen. Participants are instructed to monitor the digits for strings of three consecutive odd or three consecutive even digits. The digits are presented on the computer screen at the rate of 100 per minute in pseudo random order. The participant is instructed to respond to the target strings by pressing the space bar as quickly and as accurately as possible. The task runs for 5 minutes, with 8 correct target strings presented per minute. Scores are computed for number of correctly detected strings (hits), the average reaction time for correct detections, and number of false alarms.

5.2.6 Procedure

Participants were tested individually in single person cubicles whilst wearing ear defenders to limit any noise distractions.

The study commenced with a practice day at 8.30 am that was identical to the subsequent study visits, with the exception that no treatment was consumed (the practice visit followed that of a low effort, no dual task visit) and that this visit was completed in a lab with up to 6 participants at once, all visually isolated. Prior to completing the practice session, consent was sought and initial screening completed. Upon completion of the practice visit, participants received instructions on the secondary hand movement task which they would complete on 2 of the remaining visits and were given the opportunity to practice the hand movement sequences. Immediately afterwards, participants completed the OGTT, whereby following consumption of the 75 g glucose drink, they rested over the subsequent 2 hours, with blood glucose measured at 30 min intervals post dose.

On each of the 4 study visits, participants presented to the lab at between 8 am and 9.30 am (the same time session was attended for each visit by participants), following a minimum fast of 12 hours (this fasting was also observed prior to the practice visit and OGTT). There was a minimum duration of 48 hours between study visits. Compliance with fasting instructions was checked via completion of a food diary and verbally. Baseline mood and satiety measures were taken prior to baseline blood glucose levels. Participants then consumed the drink and rested for 15 min to allow for absorption, followed by pre-test mood and satiety measures, then pre-test blood glucose. Testing then commenced in the following order; 1) word display (+/- dual hand movement task), 2) repeated cuing/retrieval phase, 3) filler tasks (serial 3s subtractions, serial 7s subtractions & RVIP), 4) category cued word recall and 4) word pair recognition task. Post-test mood and satiety, then blood glucose levels were finally assessed (see figure 5.2a and b).

Of the possible 24 treatment/effort orders for the study day conditions, only 22 were used. Participants were randomly allocated to a set condition order, with no 2 participants completing the conditions in the same order. All stimulus sets were fixed by study day rather than condition, to minimize any practice effects or variation in difficulty affecting performance.

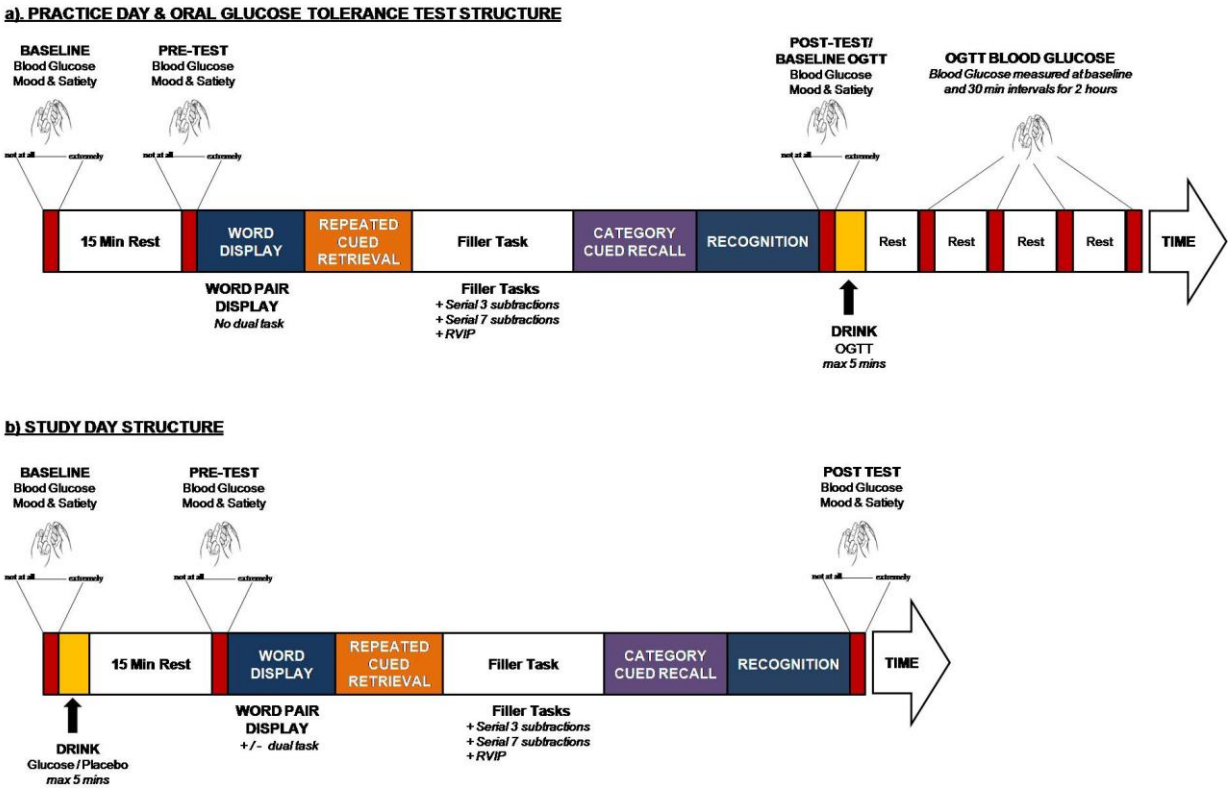


Figure 5.2 Schematic of the lab visits; *a) Practice and OGTT visit structure, and, b) Study day visit structure.*

5.2.7 Statistics

A median split was utilised to group participants into better or poorer glucoregulators on the basis of their evoked glucose at 60 min minus baseline levels from the OGTT. A two-way (Glucoregulation x Time) ANOVA was conducted on OGTT data to assess glucoregulation differences between the two groups.

Blood glucose levels on study days were analysed via a 4 way mixed (Time x Treatment x Effort x Glucoregulation) ANOVA.

A four way mixed (Treatment x Effort x Response Type x Glucoregulation) ANOVA was used to analyse outcomes from the cued recall and word recognition tasks

Filler tasks (Serial 3s, serial 7s and RVIP) were analysed using a 3 way mixed ANOVA (Treatment x Effort x Glucoregulation).

Mood and satiety measures (Bond Lader, SF STAI & VAS) were analysed via a 4 way mixed (Time x Treatment x Effort x Glucoregulation) ANOVA on change from baseline scores. One way ANOVA was used to assess any baseline differences on these measures.

Where ANOVA revealed significant findings ($p<0.05$) post hoc pairwise comparisons with a Bonferroni correction applied were completed.

5.3 Results

5.3.1 Blood Glucose Levels

5.3.1.1 Oral Glucose Tolerance Test

Analysis showed no baseline differences in poorer and better glucoregulators' glucose levels prior to consumption of the glucose load. The OGTT response curve for all participants showed the normal pattern for a cohort of healthy young adults (see figure 5.3a). A two-way ANOVA revealed a time x glucoregulation interaction ($F(4,17)=8.622$, $p=0.001$, $r=0.581$). Following post-hoc analyses poorer regulators (as grouped by the median split) were found to have significantly greater levels of circulating blood glucose levels than better regulators at; 60 min ($t(20)=4.010$, $p=0.001$), 90 min ($t(20)=3.584$, $p=0.002$) and 120 min ($t(20)=3.508$, $p=0.002$), see figure 5.3b.

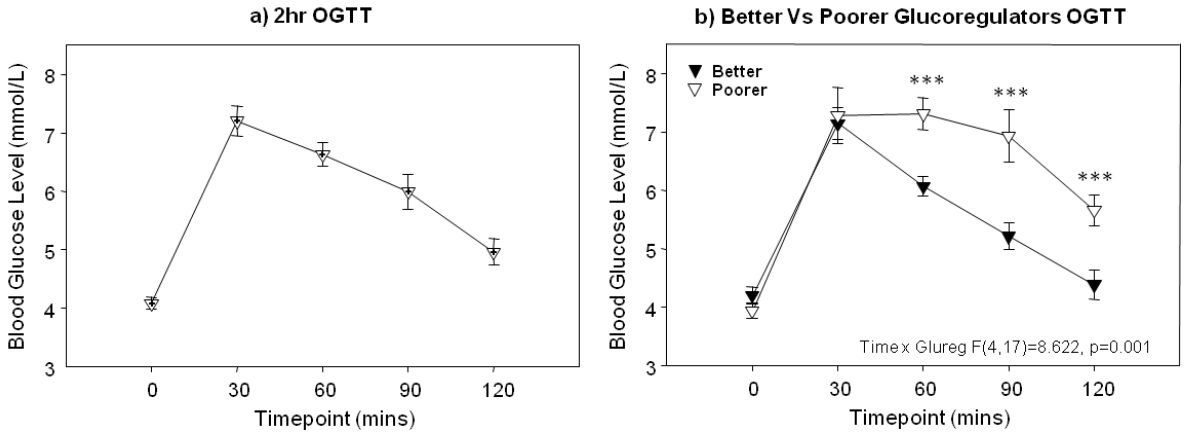


Figure 5.3 OGTT glucose levels; *a) Mean overall OGTT glucose levels and b) Better vs. poorer glucoregulators OGTT glucose levels, c)All participants mean glucose levels, and d) Better vs. poorer glucoregulators test glucose levels (High = high effort, low = low effort, ***p<0.005).*

5.3.1.2 Test Blood Glucose Levels

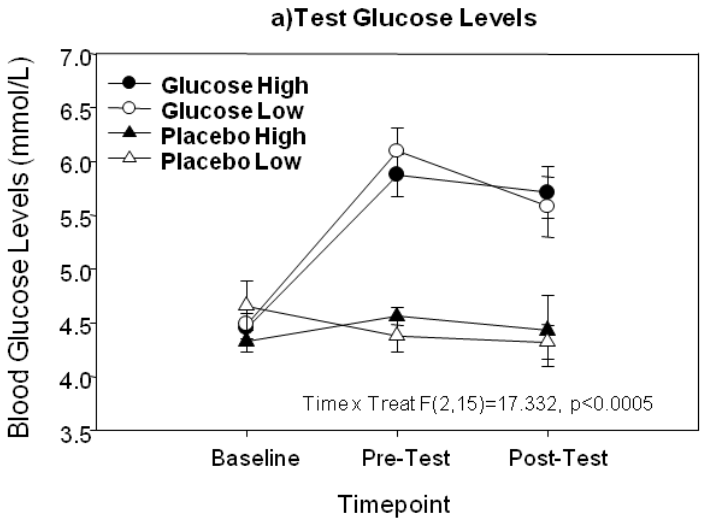
Figure 5.4a below shows the mean glucose response curves for each treatment / effort condition, with figure 5.4b showing the test glucose levels for the better and poorer glucoregulators respectively.

For blood glucose levels a treatment x time interaction ($F(2,15)=17.332$, $p<0.0005$, $r=0.732$), revealed that a glucose drink increased circulatory glucose levels at pre-test

(t(15)=9.386, p<0.001) and post-test (t(15)=4.195, p=0.001). A trend for a treatment x effort x glucoregulation interaction neared significance (F(1,16)=4.127, p=0.059, r=0.453).

Table 5.1 Means, SEM and significant effects for circulatory blood glucose levels. Significant effects and interactions are indicated in the final column *(Glureg = glucoregulation, Ti = time, Tr = treatment, [t]p<0.1*****p<0.0005).*

Outcome	Timepoint	Task Effort Level	Glucoregulation Group	*n*=	Glucose			Placebo			Significant Effects & Interactions
					Means	±	SEM	Means	±	SEM	
Blood Glucose Levels	Baseline	High	Better	9	4.70	±	0.21	4.47	±	0.14	Ti ***** Tr ***** Ti x Tr ***** Tr x Ef x Glureg [t]
			Poorer	9	4.20	±	0.17	4.20	±	0.14	
		Low	Better	9	4.73	±	0.26	4.91	±	0.44	
			Poorer	9	4.24	±	0.09	4.40	±	0.08	
	Pre-Test	High	Better	9	5.88	±	0.27	4.49	±	0.10	
			Poorer	9	5.86	±	0.32	4.42	±	0.13	
		Low	Better	9	5.96	±	0.30	4.53	±	0.27	
			Poorer	9	6.22	±	0.34	4.23	±	0.13	
	Post-Test	High	Better	9	5.92	±	0.40	4.27	±	0.10	
			Poorer	9	5.49	±	0.26	4.60	±	0.66	
		Low	Better	9	5.26	±	0.29	4.51	±	0.31	
			Poorer	9	5.91	±	0.46	4.13	±	0.10	



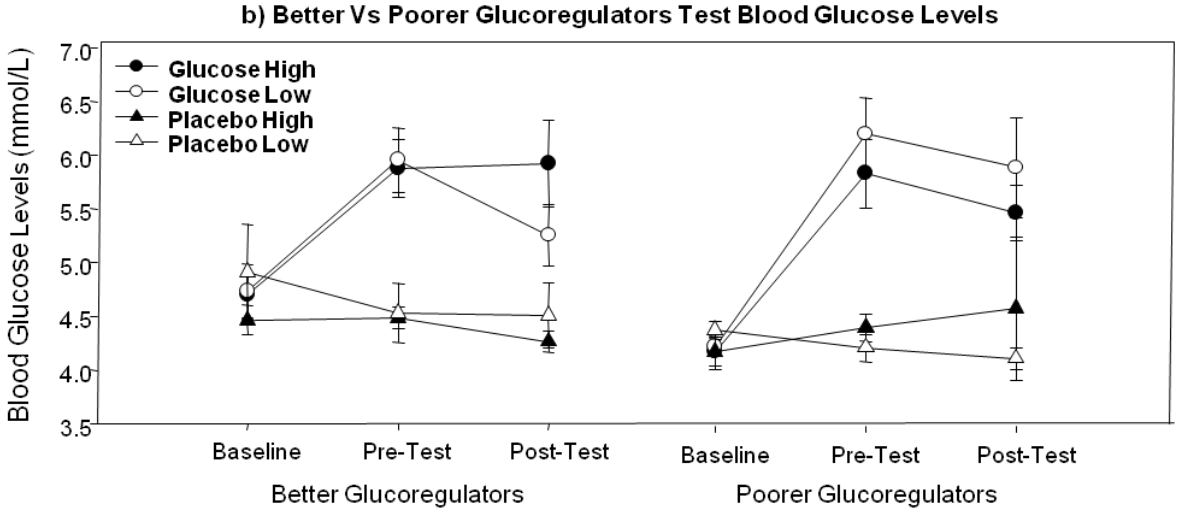


Figure 5.4 Test blood glucose levels: *a) All participants mean glucose levels, and b) Better vs. poorer glucoregulators test glucose levels (High = high effort, low = low effort).*

5.3.2 Primary Task Outcomes

Table 5.2 gives a summary of means, SEM and significant effects for the category cued recall and recognition tasks.

Table 5.2 Means, SEM and significant effects for category cued recall and recognition task outcomes. Significant effects and interactions are indicated in the final column *(Ef = effort, Glureg = glucoregulation, RType = response type, Tr = treatment, ^{t}p<0.1, *p<0.05, **p<0.01, **p<0.005, ****p<0.001,*****p<0.0005).*

Task	Outcome	Response Type	Task Effort Level	Glucoregulation Group	*n=*	Glucose			Placebo			Significant Effects & Interactions
						Means	±	SEM	Means	±	SEM	
Recall	% Recalled Overall		High	Better	10	53.33	±	7.00	49.17	±	3.77	Ef *****
				Poorer	10	52.50	±	7.14	45.83	±	7.14	
			Low	Better	10	67.50	±	5.26	70.42	±	4.63	
				Poorer	10	70.42	±	7.99	67.50	±	7.97	
	#Errors		High	Better	10	0.55	±	0.21	0.91	±	0.34	-
				Poorer	10	0.45	±	0.21	0.55	±	0.31	
			Low	Better	10	0.64	±	0.31	0.82	±	0.33	
				Poorer	10	0.55	±	0.16	0.55	±	0.28	
	% Recalled	Rp+	High	Better	10	76.67	±	6.67	88.33	±	3.56	Ef ***** Rtype ***** Ef x Rtype *****
				Poorer	10	78.33	±	10.26	78.33	±	7.05	
			Low	Better	10	88.33	±	3.56	86.67	±	4.84	
				Poorer	10	80.00	±	8.53	80.00	±	10.18	
		Rp-	High	Better	10	31.67	±	8.77	25.00	±	5.12	
				Poorer	10	38.33	±	7.47	25.00	±	9.04	
			Low	Better	10	51.67	±	8.41	60.00	±	10.00	
				Poorer	10	66.67	±	9.62	63.33	±	9.23	
		NRp	High	Better	10	52.50	±	6.81	41.67	±	6.21	
				Poorer	10	46.67	±	8.35	40.00	±	8.50	
			Low	Better	10	65.00	±	5.67	67.50	±	4.56	
				Poorer	10	67.50	±	8.28	63.33	±	7.68	
Recognition	% Correct	Rp+	High	Better	10	93.33	±	6.67	100.00	±	0.00	Ef ** Rtype ***** Ef x Rtype *** Ef x Rtype x Tr x Glureg *
				Poorer	10	88.89	±	3.93	90.74	±	4.04	
			Low	Better	10	100.00	±	0.00	86.67	±	9.72	
				Poorer	10	92.59	±	4.04	96.30	±	2.45	
		Rp-	High	Better	10	43.33	±	8.50	66.67	±	7.45	
				Poorer	10	53.70	±	11.03	40.74	±	7.91	
			Low	Better	10	73.33	±	8.50	66.67	±	9.13	
				Poorer	10	72.22	±	6.80	81.48	±	7.05	
		NRP	High	Better	10	68.33	±	6.67	71.67	±	6.24	
				Poorer	10	61.11	±	9.00	62.96	±	6.96	
			Low	Better	10	83.33	±	5.89	78.33	±	7.73	
				Poorer	10	79.63	±	5.75	83.33	±	4.81	
		Novel	High	Better	10	89.17	±	3.39	88.33	±	4.64	
				Poorer	10	88.43	±	3.73	89.81	±	3.04	
			Low	Better	10	89.17	±	3.86	90.83	±	3.58	
				Poorer	10	94.44	±	1.39	88.89	±	3.67	
	Correct RT	Rp+	High	Better	10	1074	±	113	767	±	45	Tr x Ef *
				Poorer	10	787	±	36	863	±	85	
			Low	Better	10	1111	±	240	1107	±	282	
				Poorer	10	791	±	78	888	±	62	
		Rp-	High	Better	10	1197	±	214	1222	±	97	
				Poorer	10	789	±	136	1100	±	283	
			Low	Better	10	1117	±	196	1244	±	396	
				Poorer	10	980	±	82	1152	±	132	
		NRP	High	Better	10	1768	±	574	1100	±	85	
				Poorer	10	1295	±	194	1248	±	301	
			Low	Better	10	1345	±	342	1174	±	153	
				Poorer	10	972	±	94	1140	±	223	
		Novel	High	Better	10	1345	±	213	1332	±	312	
				Poorer	10	1013	±	122	1244	±	320	
			Low	Better	10	1380	±	315	1112	±	100	
				Poorer	10	903	±	54	1352	±	265	
	Overall Incorrect RT		High	Better	10	1615	±	208	1437	±	176	-
				Poorer	10	1135	±	194	1299	±	275	
			Low	Better	10	1650	±	461	1195	±	114	
				Poorer	10	1128	±	167	1272	±	132	

5.3.2.1 Category Cued Recall

For overall correct recall a main effect of effort F(1,18)=53.505, p<0.001, r=0.865) revealed more correct items were recalled overall following low effort than high. No differences were observed on the number of errors

For proportion of correctly recalled items a response type x effort interaction (F(2,17)=14.689, p<0.001, r=0.681) revealed that following high effort a greater proportion of NRp items were recalled than Rp- (t(17)=5.579, p<0.001), with more Rp+ items recalled than both Rp- ((t17)=9.345, p<0.001) and NRp (t(17)=7.149, p<0.001). In low effort NRp and Rp- did not differ significantly, but again more Rp+ items were recalled than Rp- (t(17)=5.445, p<0.001) and NRp (t(17)=5.105, p<0.001). Whilst Rp+ level of recall did not differ with effort level, high effort reduced recall of Rp- (t(17)=6.320, p<0.001) and NRp (t(17)=5.797, p<0.001), see figure 5.5a.

For proportion of correctly recalled items a response type x glucoregulation interaction trend (F(2,17)=3.123, p=0.070, r=0.394) showed no difference between better and poorer regulators on the proportion of correct responses within each response type. However, when looking at the differences between response types isolated for better and poorer regulators, better regulators differences mirror that as shown for high effort; greater proportion of NRp than Rp- (t(17)=6.208, p<0.001), greater Rp+ than Rp- (t(17)=7.238, p<0.001) and also greater Rp+ than NRp (t(17)=5.591, p<0.001). Poorer regulators however, mirrored the effort for low effort with NRp and Rp- not significantly different (t(17)=2.578, p=0.058) but Rp+ greater than both Rp- (t(17)=5.200, p<0.001) and NRp (t(17)=4.892, p<0.001), see figure 5.5b.

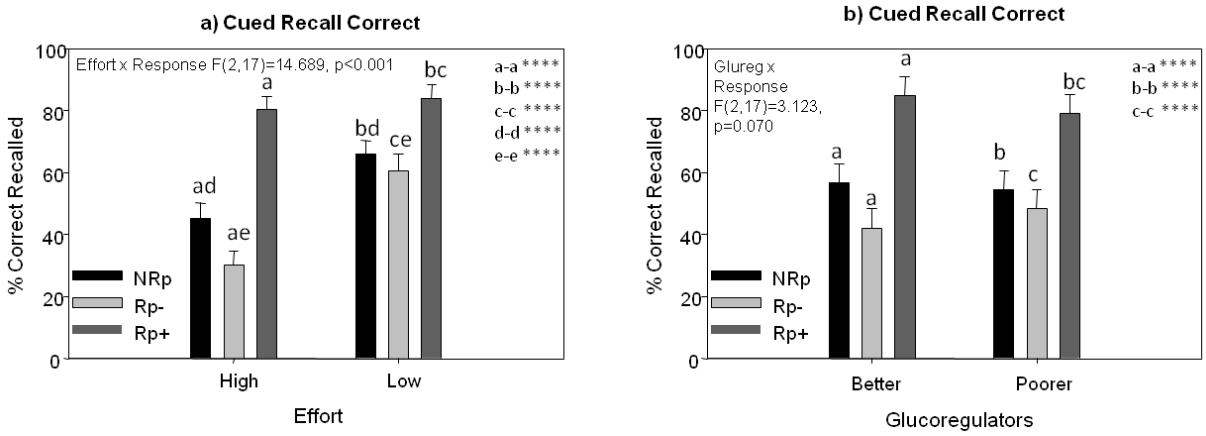


Figure 5.5 Cued Recall Interactions; *a) Effort x Response Type interaction on the proportion of correct items recalled and b) Glucoregulation x Response Type Interaction. Response types are comprised of: NRp (non practiced category), Rp+ (practiced item from practiced category) and Rp- (non practiced item from practiced category (see figure keys for significance).*

5.3.2.2 Word Recognition

Due to a data capture error, data for only 14 participants is available for this task. See table 5.2 above for a summary of means, SEM and significant effects for this task.

For correct recognitions an effort x response type interaction ($F(3,10)=9.130$, $p=0.003$, $r=0.691$) revealed that more RP+ items were correctly recognised following both high and low effort than Rp- ($t(10)=9.821$, $p<0.001$ & $t(10)=4.724$, $p=0.003$). Rp+ items were also recognised more than NRp items following high ($t(10)=10.049$, $p<0.001$ and low effort ($t(10)=3.741$, $p=0.017$) indicating a retrieval advantage of repeatedly cued items. There was no difference between NRp and novel item correct identifications in either high or low effort. Only following high effort were Rp- items recognised less than NRp ($t(10)=5.413$, $p=0.001$) which is indicative of inhibition, but Rp- items were correctly identified less than novel items in both high ($t(10)=7.274$, $p<0.001$) and low effort ($t(10)=3.968$, $p=0.011$). Finally less NRp items were correctly identified during the recognition task than novel items following high effort ($t(10)=5.596$, p0.001) indicating inhibition of non-semantically linked categories, see figure 5.6a.

For correct recognitions a 4 way treatment x effort x response type x glucoregulation interaction was also found, see figure 5.6b. Several pairwise differences were found, for ease these are displayed in tabular form along with direction, see table 5.3 below. The majority of the pairwise differences were found for poorer regulators; following the placebo treatment with high effort there was evidence of increased inhibition through fewer Rp- recognitions than NRp. Poorer regulators also failed to recognise fewer Rp- items than novel item (following glucose high effort, glucose low effort). Recognition advantages with more Rp+ items recognised than NRp were seen for; better regulators after placebo low effort, poorer regulators after glucose high effort and placebo high effort. Overall fewer Rp- items were recognised by poorer regulators after placebo high effort than low, poorer regulators also recognised fewer NRp items following high effort after glucose and placebo, indicating an overall inhibition rather than targeted inhibition.

No significant effects on reaction times were found.

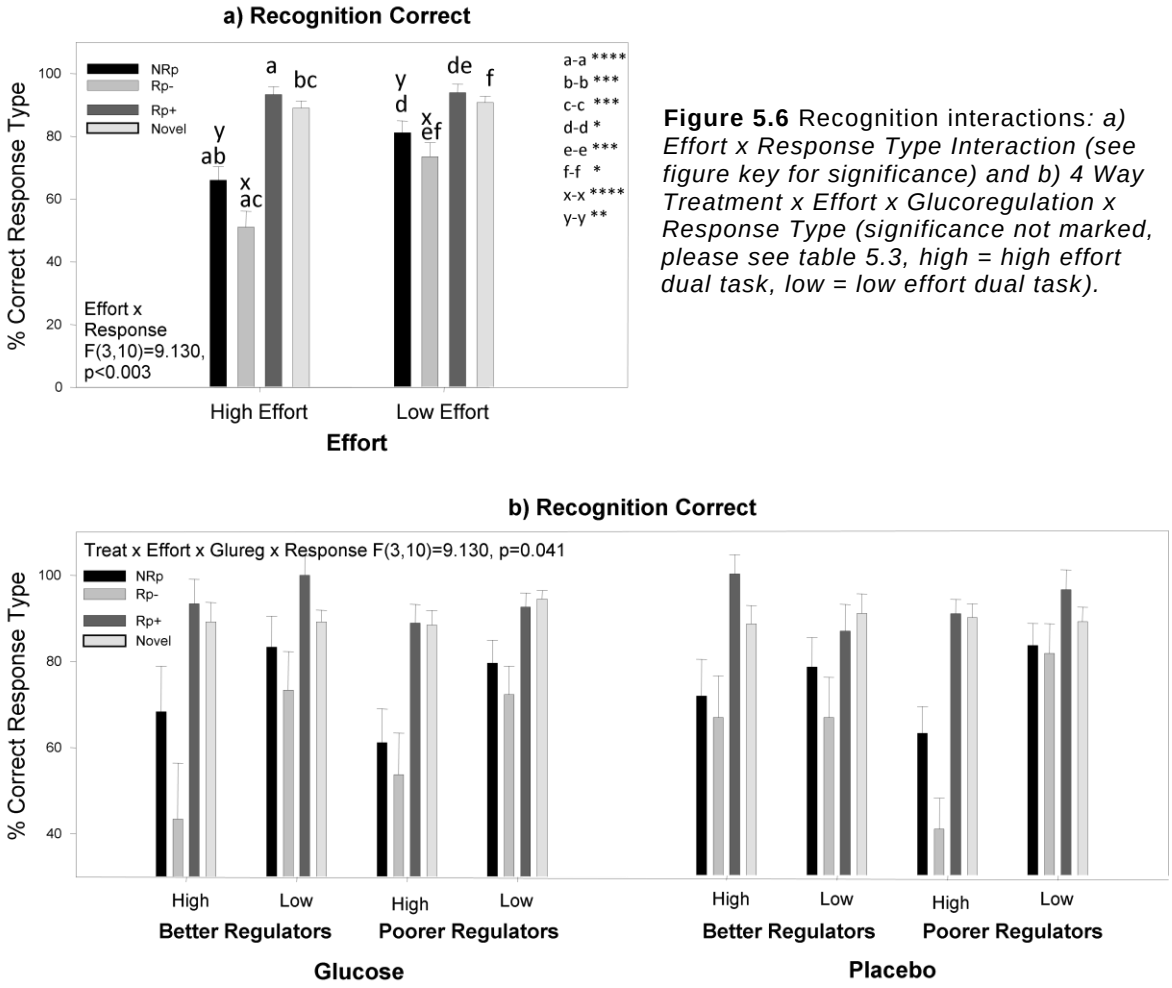


Figure 5.6 Recognition interactions*: a) Effort x Response Type Interaction (see figure key for significance) and b) 4 Way Treatment x Effort x Glucoregulation x Response Type (significance not marked, please see table 5.3, high = high effort dual task, low = low effort dual task).*

Table 5.3 Significant pairwise comparisons for the 4 way Treatment x Effort x Response Type x Glucoregulation interaction (t and p values are indicated).

Group	Pairwise Difference	t(10)=	P Value
Better Regulators, Glucose, High Effort	Rp+ > Rp-	4.658	0.003
Better Regulators, Placebo, Low Effort	Rp+ > Rp-	3.651	0.02
	Rp+ > NRp	4.007	0.01
Poorer Regulators, Glucose, High Effort	Rp+ > Rp-	4.398	0.005
	Rp+ >NRp	4.201	0.007
	Rp- < Novel	3.889	0.013
	NRp < Novel	3.414	0.031
Poorer Regulator, Glucose, Low Effort	Rp- < Novel	3.68	0.019
Poorer Regulator, Placebo, High Effort	Rp+ > Rp-	7.349	<0.001
	Rp+ > NRp	5.271	0.001
	Rp- < NRp	3.196	0.046
	NRp < Novel	4.962	0.002
Rp– responses, Poorer Regulators, Placebo	High < Low Effort	5.951	<0.001
NRp responses, Poorer Regulators, Glucose	High < Low Effort	2.219	0.047
NRp responses, Poorer Regulators, Placebo	High < Low Effort	2.503	0.028

5.3.3 Retention Period Tasks

Table 5.4 below gives the means, SEM and significant effects for the three retention period tasks; serial 3 subtractions, serial 7 subtractions and RVIP.

Table 5.4 Means, SEM and significant effects for the retention period task outcomes. Significant effects and interactions are indicated in the final column *(Ef = effort, Tr = treatment, Glureg = glucoregulation, *p<005, **p<0.01, ***p<0.005).*

Outcome	Task Effort Level	Glucoregulation Group	*n*=	Glucose			Placebo			Significant Effects & Interactions
				Means	±	SEM	Means	±	SEM	
# Responses	High	Better	10	49.10	±	3.43	50.40	±	3.58	Ef **
		Poorer	10	45.90	±	6.23	47.50	±	5.48	
	Low	Better	10	46.20	±	3.26	46.30	±	2.33	
		Poorer	10	43.60	±	4.83	41.90	±	5.28	
% Correct	High	Better	10	96.46	±	1.33	94.51	±	1.87	-
		Poorer	10	94.44	±	1.54	94.12	±	1.76	
	Low	Better	10	96.58	±	1.41	97.69	±	1.37	
		Poorer	10	95.36	±	1.69	95.00	±	1.15	
# Responses	High	Better	10	27.90	±	3.06	31.80	±	4.00	Ef *
		Poorer	10	26.50	±	4.08	28.90	±	3.75	
	Low	Better	10	25.30	±	3.63	27.50	±	2.98	
		Poorer	10	26.40	±	3.61	25.10	±	3.10	
% Correct	High	Better	10	89.72	±	3.84	87.35	±	5.29	Ef x Glureg *
		Poorer	10	85.41	±	6.25	90.54	±	3.73	
	Low	Better	10	85.62	±	3.52	86.81	±	4.26	
		Poorer	10	91.38	±	2.05	93.04	±	2.08	
#Hits	High	Better	10	17.20	±	2.91	17.20	±	3.03	-
		Poorer	9	24.22	±	3.86	23.33	±	3.38	
	Low	Better	10	17.60	±	2.29	16.50	±	2.50	
		Poorer	9	23.33	±	3.01	19.56	±	3.18	
#False Alarms	High	Better	10	9.60	±	3.09	7.20	±	1.70	-
		Poorer	9	4.22	±	0.64	4.11	±	0.98	
	Low	Better	10	4.80	±	0.95	9.00	±	3.16	
		Poorer	9	4.78	±	0.74	5.22	±	1..75	
Correct RT	High	Better	10	455	±	15	460	±	9	Ef x Glureg ** Tr x Glureg **
		Poorer	9	456	±	10	444	±	14	
	Low	Better	10	431	±	13	452	±	15	
		Poorer	9	458	±	13	457	±	9	

5.3.3.1 Serial 3s

For the number of responses made a main effect of effort ($F(1,18)=10.478$, $p=0.005$, $r=0.607$) revealed more responses were made following high effort than low, see table 5.4 above.

5.3.3.2 Serial 7s

For the number of responses made a main effect of effort (F(1,18)=6.782, p=0.018, r=0.523) revealed more responses were made following high effort than low, see table 5.4 above.

For percentage correct, an effort x glucoregulation interaction (F(1,18)=6.206, p=0.023, r=0.506), revealed poorer regulators gave a greater percentage of correct serial 7 subtractions following low effort than high (t(18)=2.294, p=0.023), see figure 5.7a.

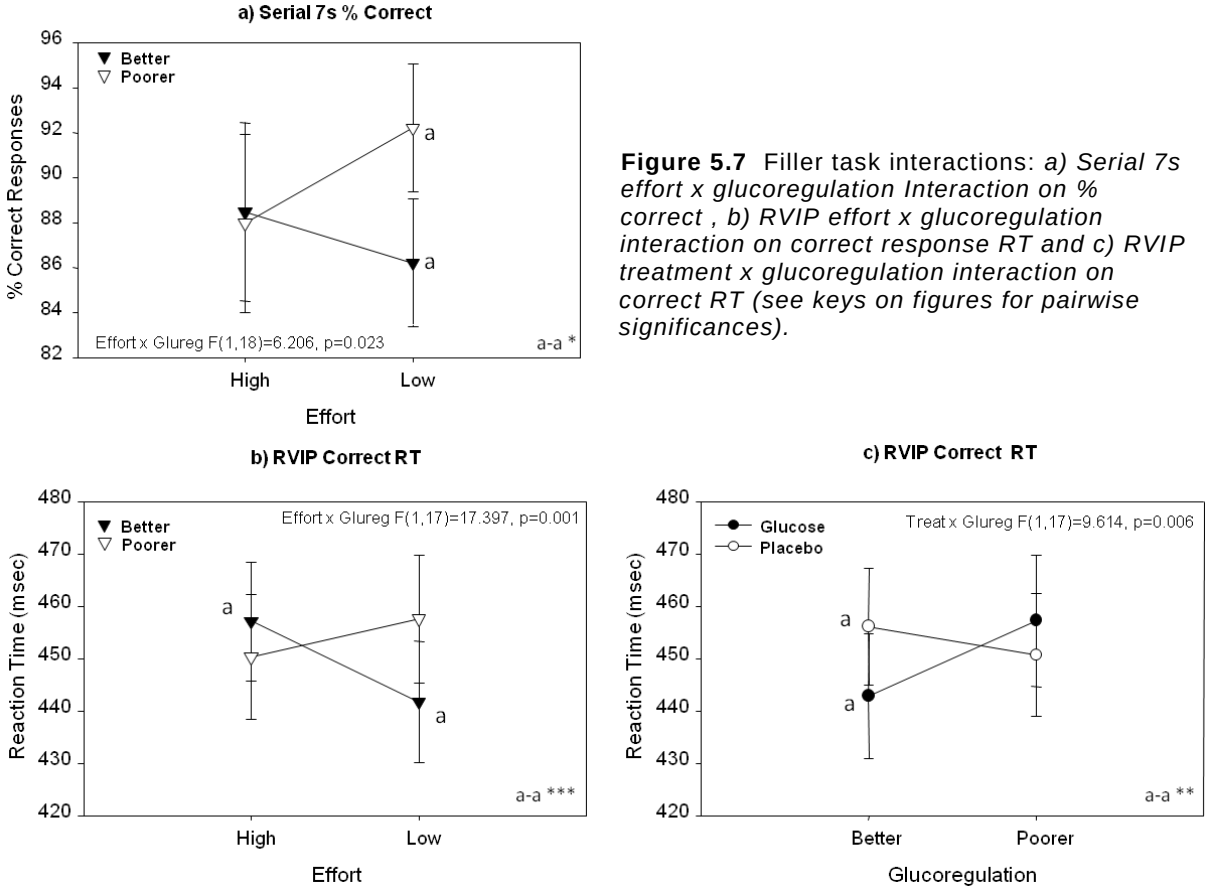


Figure 5.7 Filler task interactions: *a) Serial 7s effort x glucoregulation Interaction on % correct , b) RVIP effort x glucoregulation interaction on correct response RT and c) RVIP treatment x glucoregulation interaction on correct RT (see keys on figures for pairwise significances).*

5.3.3.3 RVIP

For hit reaction times an effort x glucoregulation interaction (F(1,17)=17.397, p=0.001, r=0.711) and a treatment x glucoregulation interaction (F(1,17)=9.614, p=0.006, r=0.601), were found. These revealed better regulators correctly responded slower after high effort than low (t(17)=4.128, p=0.001) and were also slower to respond following placebo than glucose (t(17)=3.008, p=0.008), see figures 5.7b and c.

5.3.4 Mood and Satiety Measures

Table 5.5 below gives the means, SEM and significant effects for the mood and satiety measures taken during this study.

5.3.4.1 Bond Lader

For alertness a time x glucoregulation interaction ($F(1,17)=4.879$, $p=0.041$, $r=0.472$) showed better regulators 'alertness' decreased from pre-test to post test ($t(17)=2.424$, $p=0.027$), see figure 5.8a.

For calm a time x treatment interaction ($F(1,17)=19.219$, $p<0.001$, $r=0.728$), revealed increased 'calmness' at post test following placebo ($t(17)=2.805$, $p-=0.012$), and at post test, levels of calm were significantly lower following glucose than placebo ($t(17)=4.843$, $p<0.001$), see figure 5.8b.

5.3.4.2 SF STAI

For SF STAI a time x glucoregulation interaction $F(1,18)=7.527$, $p=0.013$, $r=0.543$), revealed better regulators showed increased anxiety from pre to post test ($t(18)=2.449$, $p=0.025$), see figure 5.8c. A time x treatment interaction $F(1,18)=5.062$, $p=0.037$, $r=0.469$) was not associated with any significant pairwise differences.

5.3.4.3 VAS

For hunger a treatment x effort x glucoregulation interaction ($F(1,15)=5.041$, $p=0.040$, $r=0.502$) showed better regulators after placebo to be hungrier following high effort than low ($t(15)=2.580$, $p=0.021$), see figure 5.8d.

For thirst a 4 way treatment x effort x time x glucoregulation interaction ($F(1,15)=8.178$, $p=0.012$, $r=0.593$) showed better regulators to be thirstier at post test than poorer regulators after placebo with high effort ($t(15)=2.367$, $p=0.032$). Poorer regulators were significantly thirstier at post test following placebo with low effort than at pre-test low effort ($t(15)=2.442$, $p=0.027$) and than post test high effort ($t(15)=2.402$, $p=0.030$), see figure 5.8e.

Table 5.5 Means, SEM and significant effects for the mood and satiety measures. Significant effects and interactions are indicated in the final column *(Ef = effort, Ti = time, Tr = treatment, Glureg = glucoregulation, *p<0.05, **p<0.01, ***p<0.005, ****p<0.001, *****p<0.0005).*

Task	Outcome	Change	Task Effort Level	Glucoregulation Group	*n*=	Glucose			Placebo			Significant Effects & Interactions
						Means	±	SEM	Means	±	SEM	
SF STAI	Stress	Baseline - Pre-Test	High	Better	10	-0.30	±	0.47	-0.20	±	0.36	Ti x Glureg * Ti x Tr *
				Poorer	10	-1.00	±	0.61	-0.70	±	0.56	
			Low	Better	10	-0.40	±	0.37	-1.40	±	0.48	
				Poorer	10	-0.60	±	0.40	0.30	±	1.05	
		Baseline - Post-Test	High	Better	10	0.30	±	0.92	0.50	±	0.82	
				Poorer	10	-0.60	±	0.69	-1.20	±	0.61	
			Low	Better	10	0.60	±	0.43	-0.80	±	0.49	
				Poorer	10	-0.70	±	0.60	-1.20	±	1.16	
VAS	Hunger	Baseline - Pre-Test	High	Better	8	-6.25	±	6.03	4.50	±	4.33	Ti x Eff x Glureg *
				Poorer	9	1.11	±	3.74	0.78	±	5.44	
			Low	Better	8	5.38	±	4.09	-3.38	±	2.46	
				Poorer	9	-7.67	±	6.05	0.00	±	4.38	
		Baseline - Post-Test	High	Better	8	0.75	±	7.58	12.63	±	3.26	
				Poorer	9	4.67	±	5.69	0.67	±	3.99	
			Low	Better	8	9.25	±	4.55	-3.88	±	5.07	
				Poorer	9	-10.22	±	6.79	0.89	±	3.54	
	Thirst	Baseline - Pre-Test	High	Better	8	-9.88	±	5.33	-2.63	±	5.47	Tr x Ef x Glureg *** Ti x Tr x Eff x Glureg *
				Poorer	9	-4.67	±	3.11	-15.56	±	3.73	
			Low	Better	8	-7.88	±	7.27	-4.38	±	3.28	
				Poorer	9	-5.11	±	3.51	-7.22	±	4.43	
		Baseline - Post-Test	High	Better	8	-10.75	±	5.35	0.75	±	5.16	
				Poorer	9	2.67	±	3.66	-14.78	±	4.15	
			Low	Better	8	2.00	±	8.17	-4.25	±	4.86	
				Poorer	9	-9.67	±	4.87	0.78	±	5.59	
	Alert	Baseline - Pre-Test	High	Better	8	4.13	±	6.21	9.25	±	3.17	-
				Poorer	9	9.44	±	8.45	6.11	±	3.88	
			Low	Better	8	-0.50	±	4.42	4.75	±	3.65	
				Poorer	9	11.78	±	6.99	11.89	±	6.68	
		Baseline - Post-Test	High	Better	8	8.75	±	3.80	-0.88	±	5.42	
				Poorer	9	7.67	±	9.10	10.56	±	5.45	
			Low	Better	8	-1.00	±	7.45	4.38	±	4.41	
				Poorer	9	8.56	±	3.72	18.22	±	7.53	
	Stressed	Baseline - Pre-Test	High	Better	8	-7.63	±	4.34	1.00	±	4.78	-
				Poorer	9	-4.89	±	6.54	-1.89	±	4.01	
			Low	Better	8	0.13	±	6.46	-1.25	±	4.62	
				Poorer	9	-5.11	±	2.54	2.56	±	2.60	
		Baseline - Post-Test	High	Better	8	2.13	±	6.39	6.50	±	5.17	
				Poorer	9	-3.56	±	5.86	-1.89	±	4.49	
			Low	Better	8	-4.25	±	2.60	-0.88	±	5.73	
				Poorer	9	2.00	±	7.05	1.89	±	2.21	
Bond	Alert	Baseline - Pre-Test	High	Better	9	6.59	±	4.34	7.28	±	2.12	Ti x Glureg *
				Poorer	10	7.19	±	3.25	4.81	±	3.23	
			Low	Better	9	5.73	±	3.38	4.78	±	2.65	
				Poorer	10	5.86	±	5.05	4.81	±	2.50	
		Baseline - Post-Test	High	Better	9	4.57	±	4.05	-0.36	±	2.83	
				Poorer	10	6.90	±	4.10	5.14	±	2.58	
			Low	Better	9	3.09	±	2.26	4.85	±	2.77	
				Poorer	10	6.00	±	3.18	7.76	±	3.27	
	Content	Baseline - Pre-Test	High	Better	9	4.20	±	3.43	5.29	±	1.22	-
				Poorer	10	3.88	±	2.88	5.66	±	2.21	
			Low	Better	9	3.44	±	3.20	4.09	±	3.61	
				Poorer	10	4.88	±	1.78	1.04	±	1.35	
		Baseline - Post-Test	High	Better	9	0.33	±	1.63	-1.00	±	3.46	
				Poorer	10	1.02	±	3.35	5.24	±	1.93	
			Low	Better	9	1.49	±	2.34	3.11	±	3.71	
				Poorer	10	4.94	±	2.33	2.38	±	1.98	
	Calm	Baseline - Pre-Test	High	Better	9	-5.56	±	3.81	-2.11	±	2.60	Tr * Ti x Tr *****
				Poorer	10	-1.85	±	2.91	-3.30	±	2.24	
			Low	Better	9	-1.94	±	2.11	-1.61	±	2.29	
				Poorer	10	-0.60	±	2.04	-9.10	±	4.04	
		Baseline - Post-Test	High	Better	9	-8.94	±	3.33	-0.06	±	2.73	
				Poorer	10	0.60	±	3.54	-5.20	±	2.22	
			Low	Better	9	-4.56	±	1.21	4.85	±	2.77	
				Poorer	10	-5.30	±	2.73	7.76	±	3.27	

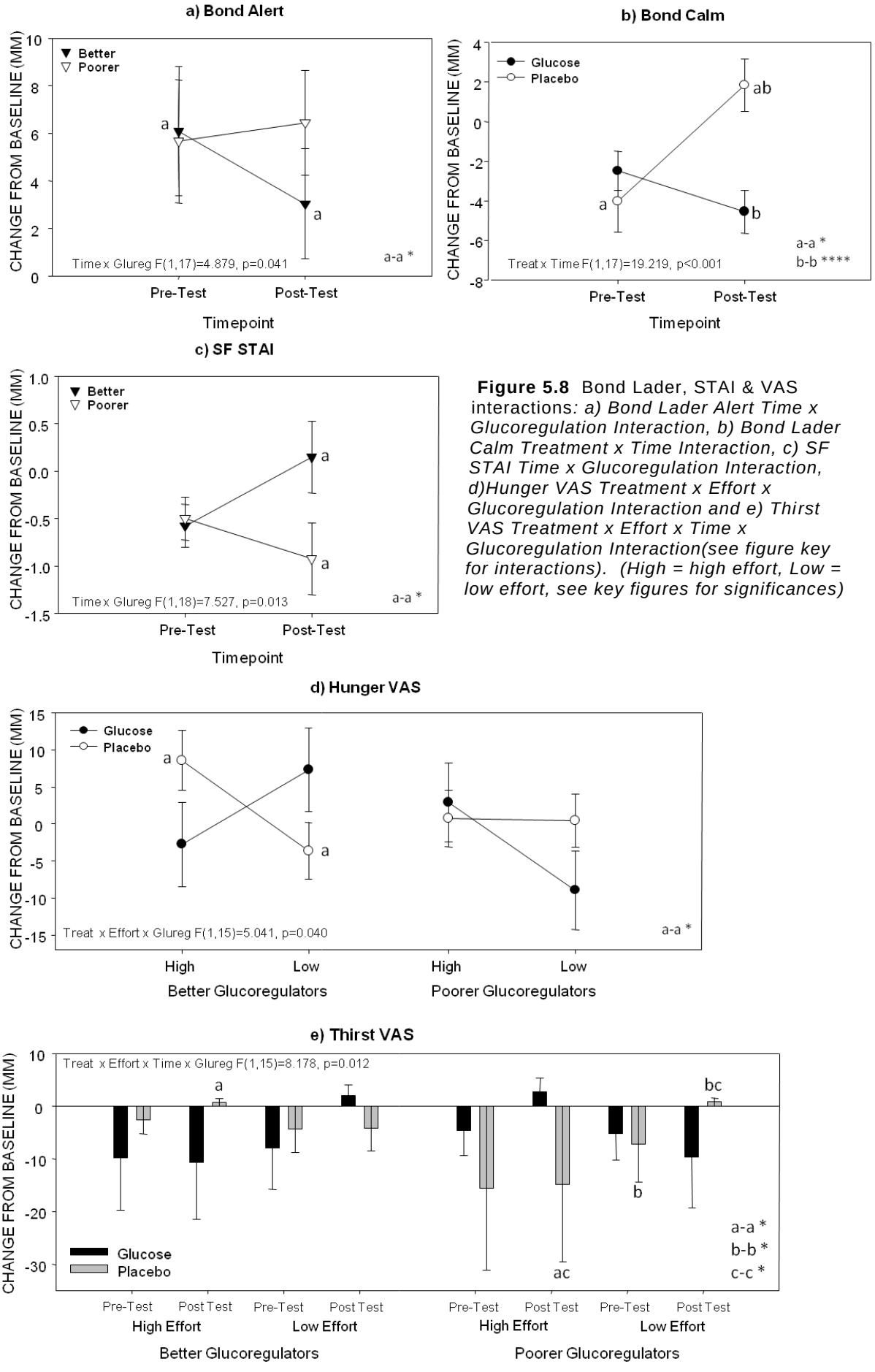


Figure 5.8 Bond Lader, STAI & VAS interactions*: a) Bond Lader Alert Time x Glucoregulation Interaction, b) Bond Lader Calm Treatment x Time Interaction, c) SF STAI Time x Glucoregulation Interaction, d)Hunger VAS Treatment x Effort x Glucoregulation Interaction and e) Thirst VAS Treatment x Effort x Time x Glucoregulation Interaction(see figure key for interactions). (High = high effort, Low = low effort, see key figures for significances)*

5.4 Discussion

5.4.1 Summary of Main Findings

This chapter aimed to address the issue of whether glucoregulation mediates inhibitory mechanisms and the potential facilitation of these mechanisms by a glucose load in conjunction with increased demand characteristics. Participants viewed high taxonomic category exemplar pairs, before repeatedly retrieving half of the items from half of the categories, via a category-letter stem completion task. Inhibition was then assessed through the number (and type) of items that were subsequently recalled during a category cued recall task.

A glucose load did not appear to influence inhibition during this paradigm. However, tentative evidence did indicate that glucoregulation does mediate inhibitory mechanisms, with only better glucoregulators displaying RIF (decreased recall of non practiced items from practiced categories). This supports the hypothesis that decrements in inhibitory control may be a feature of the memory deficits displayed in populations with poor glucoregulatory control.

Increased demand at initial encoding also seemingly increases subsequent RIF, which supports the postulation that a 'carry over' effect is acting immediately after the high effort portion of the task, which in this chapter is when the retrieval practice is completed. However, limited support is gained for a potentiating effect of glucose on this mechanism, with weak evidence hinting at a possible interaction between treatment, effort and glucoregulation in RIF.

5.4.2 Blood Glucose

Glucoregulation median splits formed two groups of regulators, whose response to the OGTT differed significantly, with the higher circulatory blood glucose levels at 60, 90 and 120 min post ingestion for poorer regulators. This suggests that this grouping does allow interpretation of the findings to be discussed in terms of assessing the performance of 2 cohorts representing a better and poorer level of the glucoregulatory response spectrum. Fasting blood glucose levels did not differ between the cohorts, and presented within normal fasting range. A treatment x time interaction on blood glucose on test visits

confirmed that a glucose drink successfully elevated circulatory blood glucose throughout the test visit.

5.4.3 Primary Outcomes

5.4.3.1 Cued Word Recall

The primary outcome of this chapter is the category cued word recall scores. Retrieval induced forgetting is manifested as fewer Rp- items recalled in comparison to NRp. Fewer NRp items recalled than Rp+, is indicative of increased availability and retrieval of practiced items. Differences in the levels of RIF between better and poorer glucoregulators would indicate that varying levels of inhibition, which is believed to be modulated by executive control in the prefrontal cortex (Johansson et al., 2007).

No treatment effects were found on any cued recall items, suggesting that administration of glucose does not elicit any performance effects on recall or inhibition in this task. No effects from any of the factors were found on the overall proportion of correct recalled items or number errors made, with only effects on the type of recall items displayed.

A significant effort x response type was found on RIF. Inhibition of Rp- items was observed following high effort but not low. A retrieval advantage for Rp+ items was seen following both low and high effort, with a decreased recall of NRp items after high effort (see figure 5.4a). A trend for a glucoregulation x response type showed only better regulators displaying RIF, with better and poorer regulators showing the Rp+ retrieval advantage (See figure 5.4b).

These findings suggest that while a glucose load does not mediate inhibition or retrieval for semantically related cued recall, cognitive demand and glucoregulation do impact on performance. The addition of a highly demanding dual task during presentation of word pairs induced greater recall for Rp+ items and decreased recall for all unpractised items (NRp & Rp-). The decreased recall in unpractised items was not uniform across Rp- and NRp items, instead there was differentially decreased recall/increased inhibition of Rp- items at recall. Better glucoregulators but not poorer regulators displayed a significantly larger magnitude of RIF, although the overall response type pattern across glucoregulators was very similar.

As inhibition increased following a high demand dual task, it may be that increased brain metabolism during the encoding phase, subsequently leads to more inhibition of competing items via a 'carry over' effect from the increased metabolism. Such an effect would increase availability of resources which could be being directed to inhibition responses. Pharmacological manipulations of nicotine have been shown to increase RIF (Rusted and Alvares, 2008). As nicotine is a cholinergic agonist, this lends support to the theory that modulation of acetylcholine in the brain may be contributing to increased RIF, which is seen as an adaptive memory facilitation.

Better regulators seemingly benefit from greater RIF regardless of the effort manipulation. This inhibition in better regulators may result from increased efficiency to effectively deploy cognitive resources to meet the demands of the task. This decreased inhibition in poorer regulators, mirrors the findings of preserved activation and decreased inhibition in ageing populations and diseases such as DAT and Schizophrenia, which also co-present with increased incidence of impaired glucoregulation.

5.4.3.2 Word Recognition

Caution must be applied to the word recognition task, as recognition was completed after category cued recall. Cued recall may exert exaggerated inhibition of items which were not recalled previously. The effort x response type interaction showed the same pattern of results as category cued recall, with RIF being evident following high but not low effort. Correct novel responses were also included as a response type, giving high correct identification rates, not differing from those seen for Rp+ responses.

A higher order significant 4 way treatment x effort x glucoregulation x response type interaction was seen during the recognition task. Whilst difficult to fully interpret, this 4 way interaction does suggest that treatment may have a role to play that was not detected via cued recall. A particularly interesting finding was that poorer glucoregulators recognised fewer Rp- items following high than low effort following placebo. This may indicate that the high effort actually benefited the poorer regulators ability to inhibit competing resources. However, generally recognition tasks are found to release items from inhibitory processes as they are redisplayed. This may not be occurring in poorer regulators, which could potentially underlie the decreased recognition of Rp- items. Such continued inhibition following re-exposure in this instance, is not adaptive since inhibiting the response is no longer beneficial.

5.4.4. Secondary Outcomes

5.4.4.1 Retention Period Tasks

For both serial 3 and serial 7 subtractions, more subtractions were made following the high effort task than low, again supporting the 'carry over' effect from increased metabolism postulated in the previous section. These results are somewhat contradictory to previous research. Glucose has been found to significantly increase the number of subtractions made in the demanding serial sevens subtraction task (2 min duration; Kennedy and Scholey, 2000, 5 min duration; Scholey et al., 2001), although no such treatment effects were observed here. Poorer glucoregulators, whilst not displaying any speed advantage, do seem to give more accurate subtractions following the low effort task, with a higher percentage of correct serial 7 subtractions being made. In poorer regulators the high effort manipulation seems to impair subsequent accuracy on serial 7 subtractions, although this finding may be attributable to type 1 errors.

During the RVIP task, better regulators were faster to generate correct responses after low effort. This could be due to less depletion of resources following low effort, which can be mobilised over the 5 minute RVIP task, although this was not observed during serial seven subtractions as may have been predicted. Better regulators also gave faster correct responses after glucose than placebo. Increased circulatory glucose seems to be preferentially targeting better glucoregulators during this sustained attention task. This would support previous findings, which have reported a glucose load to facilitate sustained attention (although this was in children) (Benton et al., 1987, Benton and Stevens, 2008). The finding that responses were made faster following low effort than high in better regulators, appears to suggest that following highly demanding tasks, the resources are no longer facilitating speeded reaction times in better glucoregulators in this task.

These filler tasks are utilised in the next chapter and will be further explored there.

5.4.4.2 Mood and Satiety

Better regulators reported a significant decrease in Bond Lader 'Alert' at post test, a finding echoed by better regulators' increased state anxiety at post test. Treatment x time interaction on Bond Lader 'Calm' showed increase calm at post test following placebo,

which at post test gave significantly higher levels of calm than did consumption of glucose. The lack of effort effects suggests that although demand and cognitive load were explicitly manipulated in this study, this did not impact upon perceived stress or anxiety throughout. Alternatively, as post test mood and satiety measures were taken some time after the high effort component of this task, perhaps any feelings of anxiety/stress had subsided prior to completion of these measures.

Self reported hunger showed better regulators reporting increased levels of hunger following placebo in the high effort condition, but decreased levels when in the low effort condition. Self reported hunger gave another complex 4 way treatment x effort x time x glucoregulation interaction. Poorer regulators reported lower thirst after high effort at post test than better regulators. Again the implications of these effects are unclear and will be addressed further in the next chapter.

5.4.5 Limitations

It is possible that although 2 different glucoregulatory cohorts were identified, the poorer regulators were not impaired as to a sufficient level to allow differential facilitation by a glucose load. As such the median split may not have allowed two genuinely different cohorts of glucoregulatory responses to be assessed. This however, seems unlikely as glucoregulatory effects were displayed on various task outcomes. It may be that the poorer glucoregulators (from a young self reported healthy adult cohort) may not be impaired to such a level as to adequately display treatment effects, or that treatment effects were present but failed to reach a large enough effect size to be detected in this relatively small sample. This may account for the lack of treatment effects observed throughout the memory tasks presented in this chapter.

5.4.6 Conclusion

This chapter tentatively concludes that glucoregulation in healthy young adults, does modulate inhibition, with poorer regulators showing decreased inhibition as predicted in the hypotheses. Clearly further work is needed to dissociate further the effects found in this chapter. The stimuli in this study were all semantically linked, enabling controlled inhibition via the RIF paradigm on specific stimuli. While this chapter has generated some interesting findings, such advantageous inhibition processes in better regulators may be specific to semantically linked categorical stimuli. Further work is required to investigate

whether such glucoregulatory inhibition responses are unique to semantically linked stimuli, or whether these findings can be generalised to active memory traces that do not share such explicit semantic links. Further investigation of paradigms tapping into similar processes will also help to elucidate whether the lack of treatment effects found here are true, or not of an adequate size to be detected in this sample. The evidence from this chapter has not generated convincing evidence that the glucose facilitation effect on memory is acting upon inhibition processes during this RIF paradigm utilising semantically related stimuli.

CHAPTER 6. AN EVALUATION OF GLUCOREGULATION AND FACILITATION EFFECTS OF GLUCOSE ON THE MEMORY BLOCKING EFFECT

6.1 Introduction

Tentative evidence from chapter 5 suggests that better glucoregulators benefit from greater retrieval induced forgetting (RIF) of semantically related material, when compared to poorer regulators. This demonstrates a greater efficiency of memory via increased suppression/inhibition of semantically related material. Evidence from chapter 4 indicated that better regulators may also exhibit advantageous control over encoding processes. Chapter 3 also indicated a possible advantage of better glucoregulators with regards to the speed at which correct recognitions were made. The evidence with regards to any glucose facilitation effect on memory has been very limited, but where effects have been observed they been more apparent in better glucoregulators and or during the high effort manipulation.

Having established subtle differences between better and poorer glucoregulators' different phases of memory, this chapter seeks to elucidate further how glucoregulation and glucose facilitation interplay with the intricacies of memory utilising the Memory Blocking Effect (MBE). While RIF assessed forgetting and suppression/inhibition of semantically related items previously encoded, the use of the MBE paradigm allows an assessment of whether the findings in chapter 5 are comparable when addressing orthographically similar but semantically dissimilar stimuli. Specifically a greater understanding as to how deficits in poorer regulators, and the potential facilitation by glucose, may be interacting with executive control, activation and suppression/inhibition. Utilising this paradigm in relation to glucose facilitation and glucoregulatory control, presents an opportunity to give further generalisation of the roles of these factors in inhibition and memory failures, as this paradigm is similar to other retrieval inhibition phenomena utilised during this thesis; directing forgetting, feeling-of-knowing (remember/know/guess), retrieval induced forgetting, in addition to further effects not investigated; tip-of-the-tongue and negative priming (Rass and Leynes, 2007, Landau and Leynes, 2006, Logan and Balota, 2003, Smith and Tindell, 1997).

A memory block (which is closely related to retrieval inhibition) is a phenomena whereby one's knowledge/memories cannot be brought to mind (Smith and Tindell, 1997). The standard memory blocking effect (MBE) paradigm was devised initially by Smith and Tindell (1997), and is a continuation of the word fragment completion test. MBE in this

paradigm refers to the interference of a negative (orthographically similar) prime on subsequent completion of a word fragment with similar orthographical features e.g. ANALOGY for fragment A_L__GY. MBE is displayed as participants perseverate on the interfering prime word even though the item cannot successfully complete the word fragment, hence impairing an individual's ability to further search for an appropriate response.

Studies investigating the implication of age as an influencing factor on this paradigm have lead to mixed findings. However, there is evidence to suggest differential response patterns during MBE between young and older ages. According to Logan and Balota (2003), older adults appear to be more susceptible to intrusions (incorrectly completing fragments with the blocking prime), even when explicitly pre-warned of this error type, whereas younger adults make more omissions (no response at all) with fewer intrusions. Older adults also completed fewer fragments across all primes, but more markedly so for blocking primes. Response latency was faster overall for young adults, but slowest for blocking fragments. This latter pattern was replicated in older adults, who also exhibited slower latencies over all primes than young adults. Results were interpreted to suggest that ageing may result in a reduced ability to control the activation of a lexical competitor when attempting to retrieve a target word, through diminished executive control. Interestingly the data discussed here from Logan and Bolata (2003), resemble the trade-off between latency and intrusions observed in early stage Alzheimer's disease patients performing Stroop task (Spieler et al., 1996). Such findings suggest that memory blocking effect is greater in older adults, who seem to encounter difficulties in overcoming the initial activation but whose inhibitory processes are seemingly spared. Young adults appear to manage this activation level better, recognising that the blocking prime is not an appropriate response but they seemingly still exhibit inhibition of orthographically similar items resulting in omissions. Such findings are not robust, with similar paradigms suggesting no differential age effects, with the exception that young participants make marginally more intrusions (Light et al., 1996). A body of research investigating inhibitory memory processes in ageing does, however, suggest that ageing does result in preserved activation but impaired inhibitory processes (Light et al., 2002, Zacks and Hasher, 1997, Zacks et al., 2000). Such inhibition deficits lead to "an elevated sensitivity to potential sources of interference, both at encoding and retrieval" (Zacks et al., 2000). Declining glucoregulation is a key feature of ageing and as such similar MBE effects may be observed not only in the elderly but also in poorer regulators. As such a glucose load in poor regulators may elicit facilitation via overcoming the perseveration on the incorrectly activated item hence decreasing intrusions.

Dividing attention while studying (encoding) the primes eliminates the memory block effect (Kinoshita and Towgood, 2001), although there were some confounding factors with the methodology used in this study. It has also been suggested that the divided attention manipulation in Kinoshita and Towgood's (2001) study may not have entirely eliminated MBE, but rather the effect size decreased to a level not detected by the limited power of this study (Leynes et al., 2008). Increasing effort and dividing attention at encoding has been shown to create a decrement in performance of healthy young adults and to prevent individuals performing at ceiling levels, hence allowing a margin for glucose administration to act and facilitate performance. Since divided attention in this paradigm eliminates/decreases MBE, it is possible that any glucose facilitation may manifest as a restoration (to some degree) of the MBE, should glucose be acting to increase efficiency via inhibiting/suppressing items orthographically similar to a recently primed item, even thought the active item is incorrect.

This paradigm offers a useful tool for studying the mechanisms underlying retrieval blocks and memory failures. Although traditionally an implicit memory task, the blocking effects of negative primes (reduced completion of fragments primed by orthographically similar items) are not eradicated by warning participants of this feature. Smith and Tindell (1997) utilised an affect rating task to mask the true implicit memory task. However, the MBE has been shown to be robust, occurring even when participants are aware of the subsequent memory task and are pre-warned of the blocking nature of the stimuli (Landau and Leynes, 2006), with equivalent effect magnitudes of prior word list exposure in both implicit and explicit memory tasks (Lustig and Hasher, 2001b, Lustig and Hasher, 2001a, Pilotti et al., 2008). This is also found when no correct fragment solutions (e.g. a positive prime fragment) are displayed as primes, as such participants would have no reason to derive that retrieval of prior information would facilitate performance on the fragment completion task. (Kinoshita and Towgood, 2001, Smith and Tindell, 1997).

The current study took the form of a repeated measures explicit memory task, with no affect rating task so that the divided attention element is not confounded. Traditionally this paradigm has made use of positive primes (e.g. BALLOON for the fragment B_L__ON, here the target word correctly completes the fragment) and neutral primes (e.g. UNICORN for fragment T_NG__T *(target=T A N G E N T),* whereby no interference is elicited. Recent studies have, however, demonstrated that positive primes are not necessary to produce MBE (Leynes et al., 2008). Taking advantage of this, no positive primes will be displayed during this study. The premise of this is to discourage participants from active retrieval from the initial word display, which may inflate the MBE, particularly since a repeated measures design is employed. So as to limit participant's knowledge of the

exact nature of this study, a word recognition task was also incorporated. The data from the word recognition task was analysed, although caution is applied as the fragment task by its nature, directs increased recall of blocked items and potentially skews recognition data.

Given the effects of age on MBE and the worsening of glucoregulation with age, it is plausible that glucoregulation may be an influencing factor of performance within this task. Additionally similar features, such as the effects of dividing attention, create an environment in which glucose facilitation may be observed. Any effect of glucose and glucoregulation upon this task will further the current programme of studies by further elucidating how/where glucoregulation and glucose facilitation may be affecting memory, specifically relating to suppression/inhibition by executive control or otherwise.

The following effects would be indicative of blocking and will be investigated in this study:

- Response Latency – increased time to generate a response to the word fragment is indicative of blocking interference
- Accuracy – decreased accuracy in completing negatively primed word fragments in comparison to other primes
- Intrusions – increased intrusions whereby the negative prime is incorrectly fitted into the word fragment
- Omissions – increased numbers of fragments with no attempted response

It is suggested that a glucose load may facilitate improved memory efficiency during the MBE paradigm. Any effects observed may be mediated by glucoregulatory control and be more prominent following the high effort dual task. Facilitation on this task may be observed in several (opposing) ways:

1) Increased memory blocking would suggest that a glucose load is 'streamlining' memory by directing resources to retrieve recently activate items, whilst inhibiting / suppressing orthographically similar items.

2) Decreased memory blocking is a further possible outcome. This may indicate (should a glucoregulation / treatment / interaction effect be present) that glucose is facilitating executive control in managing the activation of the blocking item so as to overcome the blocking effect and continue to search the lexicon for an appropriate response.

3) Alternatively poorer glucoregulators may suffer from a reduced effectiveness of executive control and/or ability to control the activation of a lexical competitor when attempting to retrieve a target word as found in ageing (Logan and Balota, 2003). Should this be the case as, poorer regulators may exhibit facilitation via a glucose load in the form of a differing response type, with a decrease in intrusions and increase in omissions, but with no such facilitation in better regulators.

6.2 Materials and Method

6.2.1 Design

A placebo-controlled, double blind, randomised, balanced crossover design was used. Various cognitive and mood/appetite outcomes were assessed. The variables were Treatment (25 g glucose or placebo) and Effort (high demand dual hand movement task or low demand no dual task). Glucoregulation was assessed using a separate Oral Glucose Tolerance Test (OGTT) and a median split used to allocate participants to better or poorer glucoregulation groups.

6.2.2 Participants

Twenty self reported healthy volunteers (10 male, mean age 23.95 yrs, *SD 5.04*) took part in this study which was approved by the Northumbria University School of Psychology and Sport Sciences Ethics Committee. Following completion of the study participants received an honorarium of £75. Prior to participation informed consent and screening were completed, ensuring all participants were in good health, free from illicit and recreation drugs including prescription and 'over-the-counter' medications (excluding contraceptives), did not suffer from any metabolic disorders such as glucose intolerance or diabetes, or any allergies that would prevent consumption of the treatments. All participants were non smokers. Demographic information and morphometric information was recorded including years in education (mean 15.45 yrs, *SD 2.01*), BMI (mean 23.60, *SD 4.62*) and WHR (mean 0.82, *SD 0.06*), see appendix 1.5 for full individual participant characteristics. Prior to each lab visit, participants fasted for a minimum of 12 hours, drinking only water over this period. Food diaries were kept for the 24 hours prior to all visits to aid fasting compliance, see appendix 3.2.

6.2.3 Blood Glucose Levels

Blood glucose levels were monitored using an Accutrend Plus diagnostic instrument and Accutrend Glucose test sticks (Roche Diagnostics, Germany). Blood glucose levels were measured via capillary finger prick at baseline, pre-test (15 min post dose) and at post test (~45 min post dose) for test visits. Measurements were also taken at these points over

the practice session to ensure participants were as habituated to the full process as possible (although no treatment was administered). Following completion of the practice session an OGTT was completed with glucose levels measured at Baseline, 30, 60, 90 and 120 min post glucose load.

6.2.4 Treatments

The glucose load for the OGTT was comprised of 75 g glucose in 250ml of water. Test treatments comprised of 25 gglucose (active) or saccharine (placebo), with 20ml Robinsons no added sugar orange cordial, made up to a volume of 200ml with water. Participants were permitted up to 5 minutes in which to consume the drink, with the end of the drink consumption time locked as 0 mins (t=0). Study day treatments were prepared by a disinterested third party in order to ensure the study remained double blind. Drinks were made the evening prior to the participants visit and were kept refrigerated overnight in sealed containers.

6.2.5 Assessment

6.2.5.1 Appetitive and Mood Scales

At baseline, 15 min post dose (pre-test) and completion of test battery (post test, approx 55 min), computerised appetitive and mood scales were completed. Participants rated 'hungry', 'thirsty', 'alert' and 'stressed' levels on a 100 mm visual analogue scale (VAS), by moving an on screen slider to the appropriate position on the scale labelled 'not at all' and 'extremely', on the left and right ends respectively, to indicate their current state for each descriptor. A computerised version of the Bond Lader (Bond and Lader, 1974) was also completed, along with the paper Short Form State Trait Anxiety Inventory (SF STAI). The SF STAI is comprised of 6 items from the full 16 item STAI (Spielberger, 1983) and has been verified (Tluczek et al., 2009, Marteau and Bekker, 1992), see appendix 4. Additionally at post test, a paper VAS for 'effortfulness' of the visit was completed.

6.2.5.2 Word Display

Forty words were presented on screen for 5 seconds with an inter-stimulus delay of 1 second. Words were presented in the centre of the screen in capitals, with a space between each character, in black text on a light grey background (See figure 6.1a). Five lists of 40 items were devised and assigned to each of the test visits. Each list comprised of 20 fragment 'blocking' items and 20 'neutral' items, presentation order of which was randomised.

Blocking items were selected from Rass and Leynes (2007) pool of 315 items, with only items previously eliciting blocking selected as negative/blocking items. Each of the 5 blocking item lists were matched for word length (range 6 to 8 letters), frequency (range 1 to 100 per million), baseline fragment completion (without any interference), and previous level of blocking so as to ensure a) a blocking effect could be elicited and b) each of the lists were equally susceptible, so as any effects could be confidently attributed to treatment/effort manipulations or glucoregulation factors. Emotional and Americanised items were not utilised.

The 20 neutral items were selected from the noun subset of the Toronto Word Pool (Friendly et al., 1982), these were randomly selected from the 220 lowest frequency nouns, to keep the frequency of the neutral items in line with the blocking items. Neutral items were then assigned to the five lists, after they were checked and amended where necessary to ensure nouns were not repetitive of/related to fragment blocking primes, nor negative emotive items so as not to induce unintentional interference.

6.2.5.3 Dual Hand Movement Task

A dual task was used to incite a performance deficit in individuals who otherwise may be performing at ceiling levels. This creates an opportunity for any facilitation by glucose or glucoregulatory effects to become apparent. Due to the nature of the memory blocking paradigm it is necessary to use a non-visual dual task, as this modality is engaged solely in the word display element in line with previous research utilising this paradigm. As such a continuous hand movement task which has previously successfully been employed in chapter 3, 5 and published literature (Foster et al., 1998, Sünram-Lea et al., 2001) was also enlisted here. Participants completed complex hand movement sequences, whilst simultaneously attending to the on screen word display. Two sequences of movements were completed; sequence 1: Fist – Chop – Slap & sequence 2: Back Slap – Chop – Fist.

One sequence of hand movements was completed for each word displayed. Four repetitions of each sequence were made before switching to the alternate sequence on every fifth word presentation. This switching between sequences ensures hand movements are monitored and do not become autonomous. Please see figure 3.2 for a photographic illustration.

Participants were advised to complete both tasks to the best of their abilities, with no advice given to prioritise one task over the other. To ensure compliance with the hand movement task, video cameras recorded movements throughout the task and these were checked. This element of the task was briefly rehearsed during the practice visit, with written reminder sheets being issued to participants during the dose absorption period on occasions when they were required to complete the dual task.

6.2.5.4 Retention Period Tasks

A 10 minute series of retention period tasks were completed immediately following word display, in order to prevent rehearsal of items. These tasks were comprised of a single completion of serial 3s subtraction, serial 7s subtraction and RVIP. These filler tasks were completed as per chapter 5, please see section 5.2.5.6 for full details.

6.2.5.5 Fragment Completion Task

Following filler tasks, participants undertook the fragment completion task. Forty word fragments were displayed in randomised order. Twenty of the fragments were comprised of 'blocked' fragments. Such items closely resemble block items displayed at word display; however, the block item does not correctly complete the fragment. Figure 6.1b shows a blocked fragment, participants previously saw B A L L O O N as per figure 6.1a. Although the previously presented 'balloon' cannot correctly complete the fragment, it is retrieved and potentially input as an intrusion. Twenty further control fragments were also interspersed with the blocked fragments. Control fragments were not related to any items previously displayed, they did not resemble nor could they be completed by the neutral items.

Fragments were displayed for 10 seconds, with participants required to complete the fragment by typing the response in a designated space below. Fragments were comprised of letters and missing letters (indicated by an underscore), with a space

between each character. Figure 6.1b below illustrates the on screen presentation of a fragment and response space. Once the last letter of the fragment was entered or 10 seconds had elapsed, any response input was locked and recorded, before the next fragment was displayed after 1 second. Should a mistake have been made pressing 'backspace' cleared any entered letters.

Response times to the first keyed input from stimuli onset were recorded in milliseconds, regardless of whether the response was subsequently cleared. Each fragment was scored as follows; correct if a legal word correctly completed the fragment, incorrect if a non legal word completed the fragment, incomplete if the fragment had not been fully completed after 10 seconds, an omission should no letters have been placed in the fragment, or as an intrusion if for a blocked fragment the blocking word had been entered. An online dictionary was used to determine if ambiguous words were legal or not. Response types were broken down into 'filler' and 'block' for the purposes of analysis. Strict scoring guidelines were followed to ensure consistent scoring of the word fragments.

6.2.5.6 Word Recognition

Eighty items were presented serially consisting of the 20 neutral and 20 'block' items from the original word presentation, along with 40 further novel nouns selected from the Toronto Word Pool (Friendly et al., 1982). They were selected randomly, but checked to ensure that they did not relate to/were not similar to items already in the list to avoid interference. Again Americanised and emotional items were excluded. Words were displayed in the centre of the screen, above which the question *'Do you recognise this word as one that was shown earlier?'* Participants were required to respond as quickly and accurately as possible via 'Z' key press for a recognition or 'M' key press for non recognition, by the appropriate index finger.

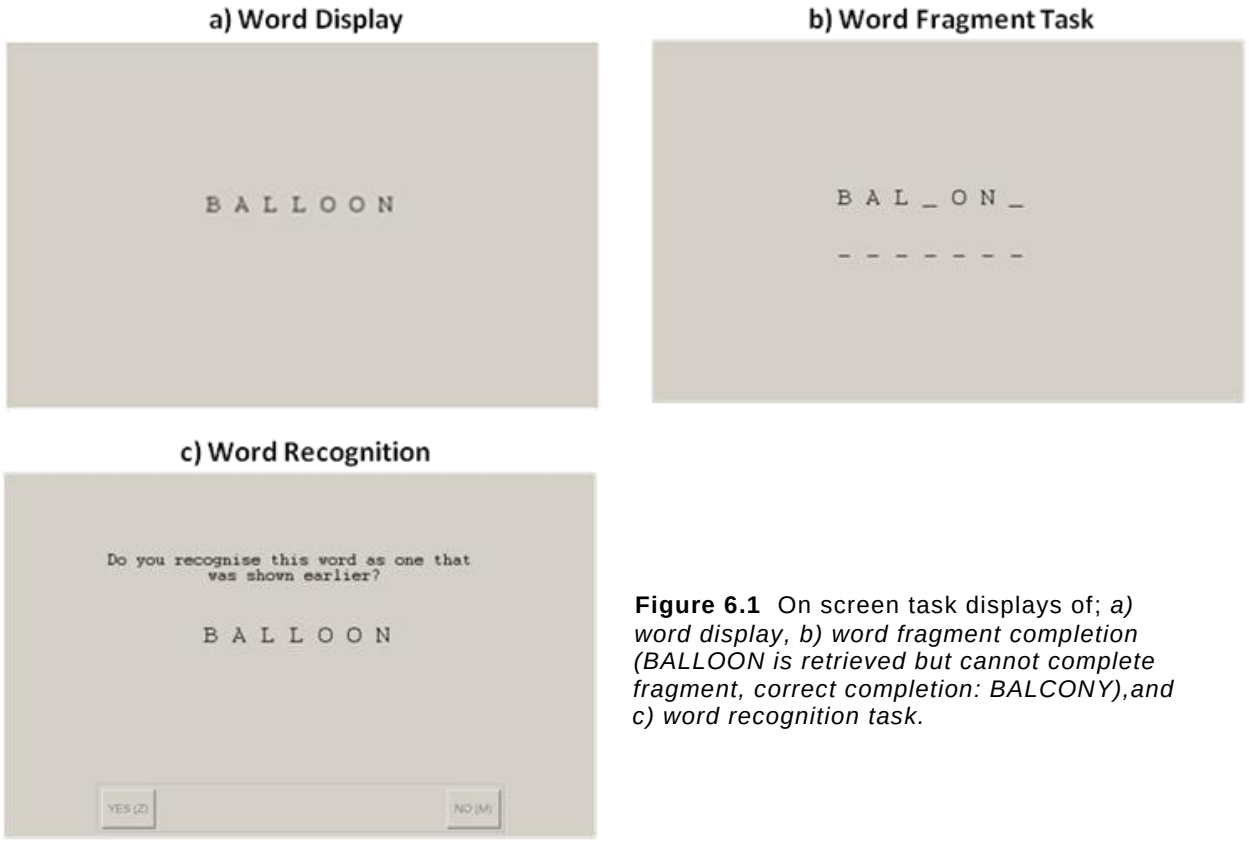


Figure 6.1 On screen task displays of; *a) word display, b) word fragment completion (BALLOON is retrieved but cannot complete fragment, correct completion: BALCONY),and c) word recognition task.*

6.2.6 Procedure

Testing was completed in a temperature controlled laboratory, in visual isolation whilst wearing ear defenders to limit any noise distractions. The study commenced with a practice day at 8.30 am that was identical to the subsequent study visits, with the exception that no treatment was consumed (the practice visit followed the procedure of a low effort, no dual task visit). Prior to completing the practice session, consent was sought and initial screening completed. Upon completion of the practice visit, participants received instructions on the secondary hand movement task which they would complete on two of the remaining visits and were given the opportunity to practice the hand movement sequences. Immediately afterwards, participants completed the OGTT, whereby following consumption of the 75 g glucose drink, they rested over the subsequent 2 hours, with blood glucose measured at 30 min intervals post dose (see figure 6.2a).

On each of the 4 study visits, participants presented to the lab at either 8 am or 9.30 am (the same time session was attended for each visit by participants), following a minimum fast of 12 hours (this fasting was also observed prior to the practice visit and OGTT). There was a minimum washout period of 48 hours between visits. Compliance with

fasting instructions was checked via completion of a food diary and verbally. Baseline mood and satiety measures were taken prior to baseline blood glucose levels. Participants then consumed the drink and rested for 15 min to allow for absorption, followed by pre-test mood and satiety measures, then pre-test blood glucose. Testing then commenced in the following order; 1) word display (+/- dual hand movement task), 2) filler tasks (serial 3s subtractions, serial 7s subtractions and RVIP), 3) word fragment completion task, and 4) word recognition task. Post-test mood and satiety, then blood glucose levels were finally assessed (see figure 6.2b).

Of the possible 24 treatment/effort orders for the study day conditions, only 20 were used, such that each of the 4 treatment/effort combinations were completed equally across study days, i.e. each condition was completed on the 1st , 2nd, 3rd and 4th study days by 5 participants. Participants were randomly allocated to a set condition order, with no 2 participants completing the conditions in the same order. All stimuli were attached to the study day not condition, to minimize any practice effects or variation in difficulty affecting performance.

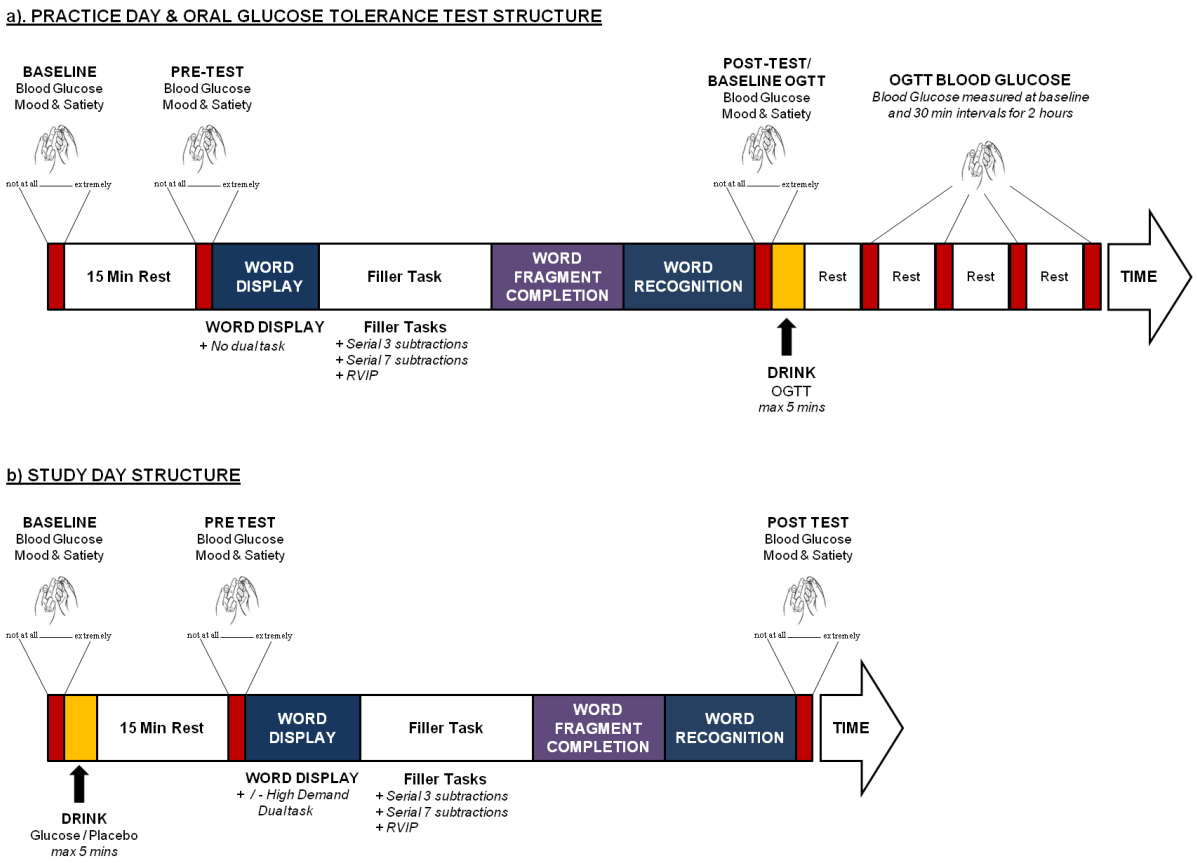


Figure 6.2 A schematic of the study day visit structure; *a) Practice and OGTT visit structure, and, b) Study day visit structure.*

6.2.7 Statistics

A median split was utilised to group participants into better or poorer glucoregulators on the basis of circulatory glucose levels at 60 min minus baseline levels from the OGTT. A two-way (Glucoregulation x Time) ANOVA was conducted on OGTT data to assess glucoregulation differences between the two groups.

Blood glucose levels on study days were analysed via a 4 way mixed (Time x Treatment x Effort x Glucoregulation) ANOVA.

A three way mixed (Treatment x Effort x Glucoregulation) ANOVA was used to analyse outcomes from the memory tasks, filler (Serial 3s, serial 7s and RVIP) tasks and tertiary effortfulness VAS.

Mood and satiety measures (Bond Lader, SF STAI and VAS) were analysed via a 4 way mixed (Time x Treatment x Effort x Glucoregulation) ANOVA on change from baseline scores. One way ANOVA was used to assess any baseline differences on these measures.

Where ANOVA revealed significant findings ($p<0.05$) post hoc pairwise comparisons with Bonferroni correction applied were completed.

6.3 Results

6.3.1 Blood Glucose Levels

6.3.1.1 Oral Glucose Tolerance Test

Analysis showed no baseline differences in poorer and better glucoregulators' glucose levels prior to consumption of the glucose load. The OGTT response curve for all participants showed the normal pattern for a cohort of healthy young adults (see figure 6.3a). A two-way ANOVA revealed a time x glucoregulation interaction ($F(4,15)=6.180$, $p=0.004$, $r=0.540$). Following post-hoc analyses poorer regulators (as grouped by the median split) were found to have significantly greater levels of circulating blood glucose levels than better regulators at; 60 min ($t(18)=4.494$, $p<0.001$), 90 min ($t(18)=2.826$, $p=0.011$) and 120 min ($t(18)=2.698$, $p=0.015$), see figure 6.3b.

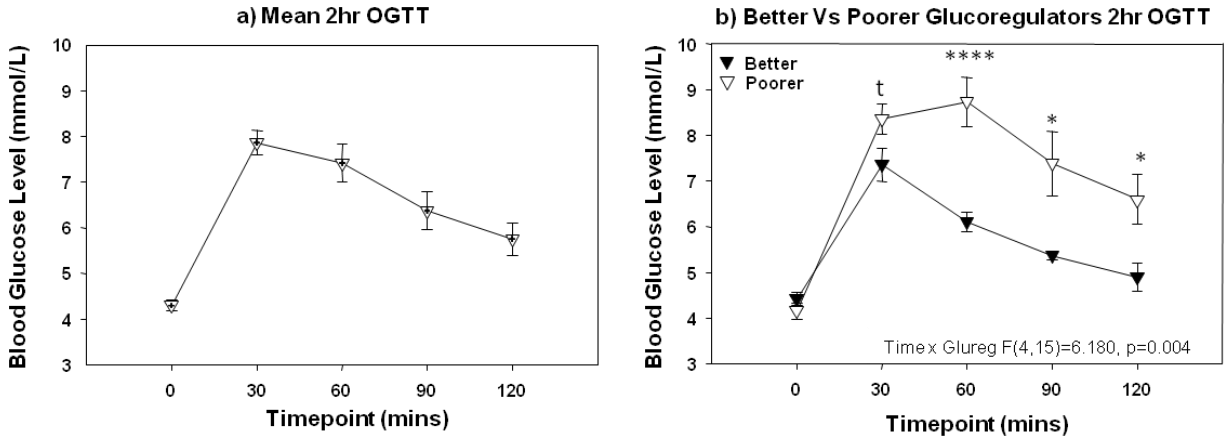


Figure 6.3 OGTT blood glucose levels; *a) Mean overall OGTT glucose levels, and b) Better vs. poorer glucoregulators OGTT glucose levels ($^{t}p<0.1$, *p<0.05, ****p<0.001).*

6.3.1.2 Test Blood Glucose Levels

Table 6.1 below gives the means, SEM and significant effects for the test visit blood glucose levels.

Table 6.1 Means, SEM and significant effects for circulatory blood glucose levels. Significant effects and interactions are indicated in the final column *(Ef = effort, Ti = time, Tr = treatment, *p<0.05, *****p<0.0005).*

Outcome	Timepoint	Task Effort Level	Glucoregulation Group	*n*=	Glucose			Placebo			Significant Effects & Interactions
					Means	±	SEM	Means	±	SEM	
Blood Glucose Levels	Baseline	High	Better	9	4.13	±	0.15	4.22	±	0.10	EF * Ti ***** Tr ***** Ti x Tr *****
			Poorer	9	4.17	±	0.12	4.20	±	0.11	
		Low	Better	9	4.24	±	0.11	4.57	±	0.18	
			Poorer	9	4.29	±	0.23	4.28	±	0.18	
	Pre-Test	High	Better	9	5.50	±	0.31	4.57	±	0.29	
			Poorer	9	5.76	±	0.28	4.18	±	0.11	
		Low	Better	9	6.08	±	0.26	4.30	±	0.16	
			Poorer	9	6.28	±	0.19	4.30	±	0.18	
	Post-Test	High	Better	9	5.73	±	0.42	4.41	±	0.23	
			Poorer	9	6.16	±	0.43	4.06	±	0.11	
		Low	Better	9	5.91	±	0.30	4.13	±	0.11	
			Poorer	9	6.73	±	0.43	4.38	±	0.29	

Figure 6.4a below shows the mean glucose response curves for each treatment / effort condition, with figure 6.4b and 6.4c showing the test glucose levels for the better and poorer glucoregulators respectively.

Glucoregulation did not significantly impact on circulatory blood glucose, however, high effort significantly reduced glucose levels ($F(1,16)=5.256$, $p=0.036$, $r=0.497$) in comparison to low effort. A treatment x time interaction ($F(2,15)=70.244$, $p<0.001$, $r=0.908$), revealed that a glucose drink increased circulatory glucose levels at pre-test ($t(16)=12.578$, $p<0.001$) and post-test ($t(16)=8.216$, $p<0.001$).

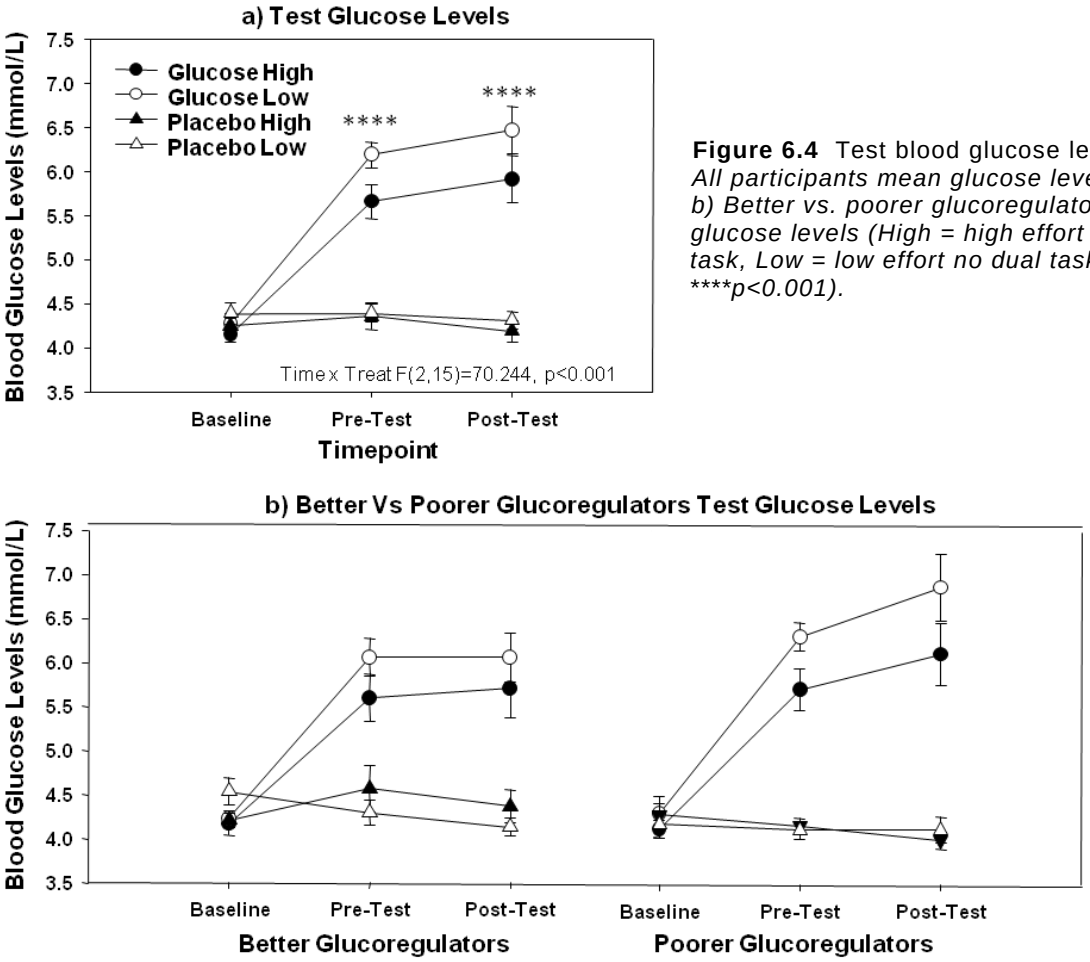


Figure 6.4 Test blood glucose levels; *a) All participants mean glucose levels, and b) Better vs. poorer glucoregulators glucose levels (High = high effort dual task, Low = low effort no dual task, ****p<0.001).*

6.3.2 Word Fragment Completion

Table 6.2 below gives the means, SEM and significant effects for the word fragment completion task.

Table 6.2 Mean scores and SEM for outcomes of the word fragment task. Significant effects and interactions are indicated in the final column (*Ef = Effort, Tr = Treatment, Glureg = Glucoregulation, *p<0.05,**p<0.01).*

Task	Outcome	Task Effort Level	Glucoregulation Group	*n*=	Glucose			Placebo			Significant Effects & Interactions
					Means	±	SEM	Means	±	SEM	
OVERALL	#Correct	High	Better	10	15.60	±	2.08	16.90	±	1.50	-
			Poorer	10	14.10	±	1.81	15.20	±	1.77	
		Low	Better	10	16.20	±	1.34	16.20	±	1.34	
			Poorer	10	13.10	±	2.02	13.10	±	2.02	
	#Omission (overall)	High	Better	10	9.90	±	2.75	8.30	±	2.36	-
			Poorer	10	4.00	±	1.84	4.80	±	2.34	
		Low	Better	10	8.60	±	2.33	8.60	±	2.33	
			Poorer	10	6.20	±	2.14	6.20	±	2.14	
	Mean RT(overall)	High	Better	10	4047	±	386	3791	±	395	Glureg *
			Poorer	10	2673	±	226	2739	±	370	
		Low	Better	10	4138	±	387	4138	±	387	
			Poorer	10	2865	±	228	2865	±	228	
	Correct RT(overall)	High	Better	10	3484	±	309	3333	±	341	Glureg *
			Poorer	10	2543	±	231	2707	±	347	
		Low	Better	10	3581	±	371	3581	±	371	
			Poorer	10	2721	±	288	2721	±	288	
	Incorrect RT(Overall)	High	Better	10	4811	±	542	4537	±	604	Glureg **
			Poorer	10	2888	±	310	2799	±	461	
		Low	Better	10	4976	±	550	4976	±	550	
			Poorer	10	2972	±	209	2972	±	209	
BLOCKED FRAGMENTS	#Intrusions	High	Better	10	1.60	±	0.75	1.30	±	0.62	Ef x Glureg *
			Poorer	10	2.40	±	0.79	2.50	±	0.60	
		Low	Better	10	1.30	±	0.47	1.30	±	0.47	
			Poorer	10	4.50	±	1.07	4.50	±	1.07	
	#Blocked Fragment Correct Responses	High	Better	10	6.70	±	1.00	6.80	±	0.94	-
			Poorer	10	6.10	±	1.00	7.00	±	0.93	
		Low	Better	10	6.90	±	0.86	6.90	±	0.86	
			Poorer	10	5.80	±	0.95	5.80	±	0.95	
	#Blocked Fragment Omissions	High	Better	10	5.20	±	1.55	4.60	±	1.57	-
			Poorer	10	1.90	±	1.05	2.40	±	0.99	
		Low	Better	10	5.10	±	1.40	5.10	±	1.40	
			Poorer	10	2.80	±	0.89	2.80	±	0.89	
	Block Overcome RT(BLOCK)	High	Better	10	3608	±	334	3409	±	409	-
			Poorer	9	2950	±	373	2652	±	431	
		Low	Better	10	3632	±	387	3632	±	387	
			Poorer	9	2870	±	385	2870	±	385	
	Mean Blocked Fragment RT	High	Better	10	4097	±	456	3943	±	502	Glureg *
			Poorer	10	2697	±	245	2665	±	378	
		Low	Better	10	4134	±	470	4134	±	470	
			Poorer	10	2859	±	248	2859	±	248	
FILLER FRAGMENTS	#FILLER CORRECT	High	Better	10	9.00	±	1.30	10.20	±	0.84	Ef *
			Poorer	10	8.00	±	0.88	8.20	±	1.05	
		Low	Better	10	9.40	±	0.91	9.40	±	0.91	
			Poorer	10	7.40	±	1.21	7.40	±	1.21	
	Overall Mean FILLERS RT	High	Better	10	4025	±	359	3712	±	353	Glureg *
			Poorer	10	2650	±	218	2803	±	358	
		Low	Better	10	4169	±	330	4169	±	330	
			Poorer	10	2862	±	243	2862	±	243	
	Mean FILLERS Correct RT	High	Better	10	3388	±	324	3269	±	307	Glureg *
			Poorer	10	2309	±	160	2686	±	350	
		Low	Better	10	3484	±	392	3484	±	392	
			Poorer	10	2672	±	263	2672	±	263	
	Mean FILLERS Incorrect RT	High	Better	9	4933	±	707	4010	±	516	Ef x Glureg * glureg x Tr *
			Poorer	9	2169	±	191	2221	±	237	
		Low	Better	9	4707	±	507	4707	±	507	
			Poorer	9	2507	±	325	2507	±	325	

Better glucoregulators demonstrated slower response times across fragment responses; overall mean RT ($F(1,18)=7.786$, $p=0.012$, $r=0.549$), overall correct responses RT ($F(1,18)=4.634$, $p=0.045$, $r=0.452$) and incorrect responses RT ($F(1,18)=9.846$, $p=0.006$, $r=0.595$). Although overall there were no apparent differences between better and poorer regulators on overall task accuracy.

For the number of intrusions an effort x glucoregulation interaction ($F(1,18)=4.594$, $p=0.046$, $r=0.451$), revealed following low effort, poorer glucoregulators suffered more intrusions than better regulators ($t(18)=2.641$, $p=0.017$), with poorer regulators also displaying significantly more intrusions following the low effort than high effort condition ($t(18)=2.558$, $p=0.020$), see figure 6.5a. A main effect of glucoregulation on blocked fragment RT ($F(1,18)=8.120$, $p=0.011$, $r=0.558$), showed better regulators were slower to attempt responses to blocked fragments.

For correct filler fragments, a main effect of effort ($F(1,18)=5.394$, $p=0.032$, $r=0.480$) revealed more correct responses were given following high than low effort. For filler fragments, main effects of glucoregulation showed better glucoregulators responding slower to filler fragments overall ($F(1,18)=3.568$, $p=0.017$, $r=0.528$) and when correct responses were submitted ($F(1,18)=4.692$, $p=0.044$, $r=0.455$). For incorrect filler fragment response RT, a treatment x glucoregulation interaction ($F(1,16)=5.093$, $p=0.038$, $r=0.491$) revealed better regulators were significantly slower to respond than poorer regulators following glucose ($t(16)=3.958$, $p=0.001$). Better regulators were also slower to give incorrect filler responses following glucose than placebo ($t(16)=2.288$, $p=0.036$), see figure 6.5b. A significant effort x glucoregulation interaction on incorrect filler fragment RT ($F(1,16)=5.143$, $p=0.038$, $r=0.493$), showed slower RT for poorer regulators following low than high effort ($t(16)=2.479$, $p=0.025$), better regulators being slower in low effort than poorer regulators ($t(16)=2.290$, $p=0.036$) and also following high effort ($t(16)=3.873$, $p=0.001$), see figure 6.5c.

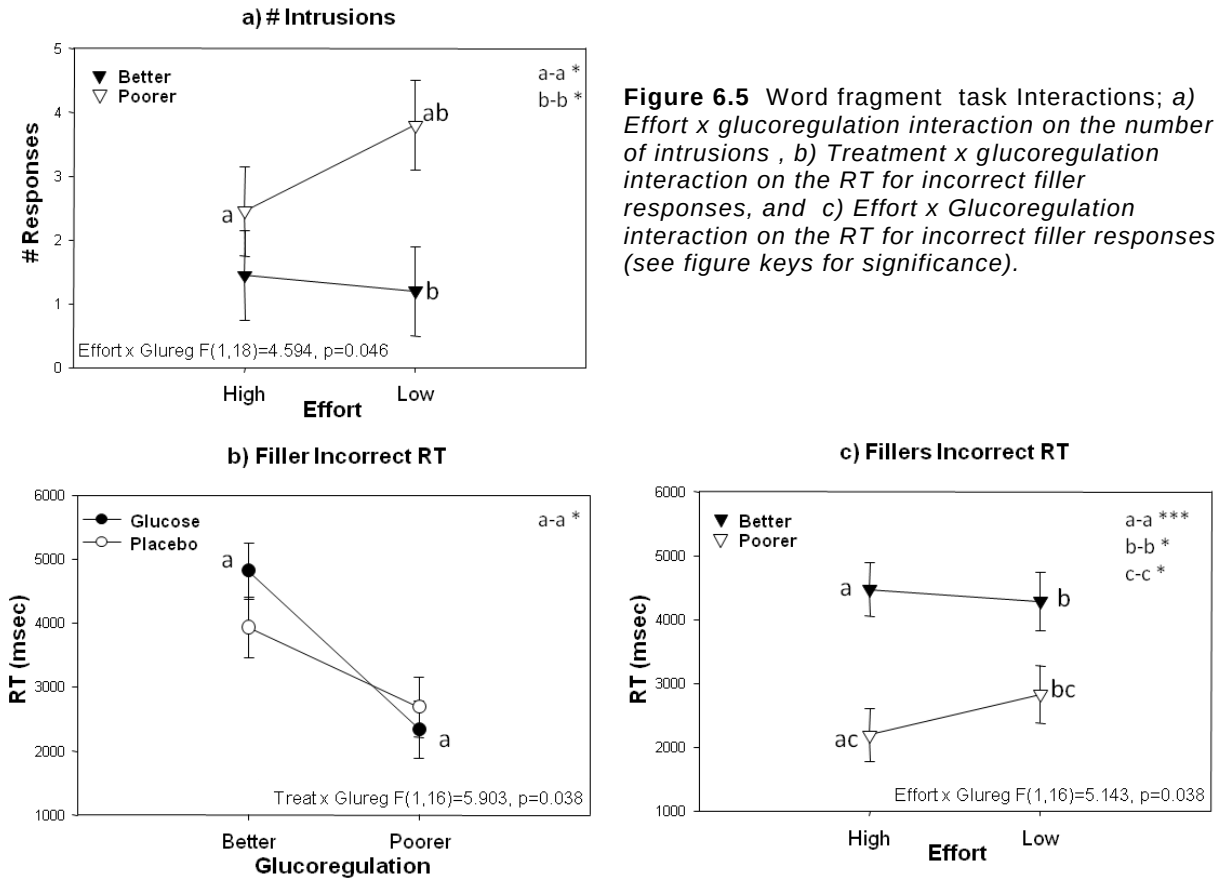


Figure 6.5 Word fragment task Interactions; *a) Effort x glucoregulation interaction on the number of intrusions , b) Treatment x glucoregulation interaction on the RT for incorrect filler responses, and c) Effort x Glucoregulation interaction on the RT for incorrect filler responses (see figure keys for significance).*

6.3.3 Word Recognition

Table 6.3 below gives the means, SEM and significant effects for the filled retention period tasks

For correctly recognised, more words were recognised following low effort than high ($F(1,18)=21.370$, $p<0.001$, $r=0.737$). This was also the case for correct recognitions of blocking words ($F(1,18)=12.752$, $p=0.002$, $r=0.644$).

Table 6.3 Mean scores and SEM for outcomes of the word recognition task. Significant effects and interactions are indicated in the final column (*Ef = Effort, ***p<0.005, *****p<0.0005)*

Outcome	Task Effort Level	Glucoregulation Group	*n*=	Glucose			Placebo			Significant Effects & Interactions
				Means	±	SEM	Means	±	SEM	
% Correct	High	Better	10	68.88	±	3.83	74.13	±	4.35	Ef *****
		Poorer	10	65.00	±	3.48	63.38	±	2.84	
	Low	Better	10	80.25	±	4.49	80.25	±	4.49	
		Poorer	10	75.25	±	3.32	75.25	±	3.32	
Correct RT	High	Better	10	968	±	68	978	±	66	-
		Poorer	10	975	±	81	989	±	85	
	Low	Better	10	896	±	67	896	±	67	
		Poorer	10	1011	±	60	1011	±	60	
Incorrect RT	High	Better	10	1039	±	93	1061	±	86	-
		Poorer	10	1087	±	62	1100	±	111	
	Low	Better	10	1260	±	271	1260	±	271	
		Poorer	10	1231	±	133	1231	±	133	
% Block Items Recognised	High	Better	10	60.00	±	7.56	67.00	±	6.46	Ef ***
		Poorer	10	58.50	±	6.71	60.00	±	6.24	
	Low	Better	10	79.00	±	4.88	79.00	±	4.88	
		Poorer	10	69.50	±	4.80	69.50	±	4.80	
Correct Block Recognition RT	High	Better	10	944	±	86	930	±	63	-
		Poorer	10	1033	±	96	1054	±	70	
	Low	Better	10	913	±	69	913	±	69	
		Poorer	10	980	±	62	980	±	62	
Incorrect Block Recognition RT	High	Better	7	976	±	142	1061	±	151	-
		Poorer	10	1105	±	102	1148	±	198	
	Low	Better	7	1563	±	459	1563	±	459	
		Poorer	10	1328	±	192	1328	±	192	

6.3.4 Filled Retention Period Tasks

Table 6.4 below gives the means, SEM and significant effects for the filled retention period tasks.

6.3.4.1 Serial 3s

For the number of responses there was an effort x glucoregulation interaction ($F(1,17)=6.049$, $p=0.025$, $r=0.512$), with pairwise comparisons revealing poorer glucoregulators made more responses following high effort than low ($t(17)=2.322$, $p=0.033$), see figure 6.6a.

Table 6.4 Mean scores and SEM for outcomes of the filled retention period tasks. Significant effects and interactions are indicated in the final column (*Ef = Effort, Glureg = gluco=regulation, Tr = treatment, *p<0.05).*

Task	Outcome	Task Effort Level	Glucoregulation Group	*n=*	Glucose			Placebo			Significant Effects & Interactions
					Means	±	SEM	Means	±	SEM	
Serial 3s	# Responses	High	Better	10	45.20	±	2.84	42.40	±	3.90	Ef x Glureg *
			Poorer	9	55.33	±	8.20	49.67	±	7.87	
		Low	Better	10	45.40	±	2.93	45.40	±	2.93	
			Poorer	9	47.67	±	7.51	47.67	±	7.51	
	% Correct	High	Better	10	96.43	±	1.27	97.54	±	0.82	-
			Poorer	9	93.50	±	1.49	93.02	±	3.38	
		Low	Better	10	97.06	±	1.22	97.06	±	1.22	
			Poorer	9	96.07	±	1.63	96.07	±	1.63	
Serial 7s	# Responses	High	Better	10	26.40	±	1.96	26.50	±	2.73	Tr x Glureg *
			Poorer	9	32.67	±	6.75	29.78	±	6.89	
		Low	Better	10	25.60	±	2.26	25.60	±	2.26	
			Poorer	9	32.22	±	6.69	32.22	±	6.69	
	% Correct	High	Better	10	90.51	±	2.86	94.17	±	2.63	Ef x Glureg *
			Poorer	9	85.18	±	4.41	87.10	±	3.89	
		Low	Better	10	89.26	±	3.66	89.26	±	3.66	
			Poorer	9	94.25	±	2.09	94.25	±	2.09	
RVIP	#Hits	High	Better	10	21.80	±	2.44	19.20	±	2.92	-
			Poorer	8	18.63	±	2.60	17.38	±	2.65	
		Low	Better	10	20.90	±	2.78	20.90	±	2.78	
			Poorer	8	17.38	±	2.90	17.38	±	2.90	
	#False Alarms	High	Better	10	7.80	±	1.63	10.30	±	3.42	-
			Poorer	8	5.88	±	1.34	6.75	±	1.72	
		Low	Better	10	7.80	±	2.77	7.80	±	2.77	
			Poorer	8	6.13	±	1.48	6.13	±	1.48	
	Correct RT	High	Better	10	423	±	8	422	±	11	-
			Poorer	8	441	±	13	438	±	10	
		Low	Better	10	440	±	10	440	±	10	
			Poorer	8	448	±	15	448	±	15	

6.3.4.2 Serial 7s

For the number of responses there was a treatment x glucoregulation interaction ($F(1,17)=6.374$, $p=0.022$, $r=0.522$), with pairwise comparisons revealing poorer glucoregulators made more responses following glucose than placebo ($t(17)=2.941$, $p=0.009$), see figure 6.6b. For the percentage of correct Serial 7 subtractions there was an effort x glucoregulation interaction ($F(1,17)=6.635$, $p=0.020$, $r=0.530$). Pairwise comparisons revealed poorer regulators to have greater accuracy following low effort than high ($t(17)=2.715$, $p=0.015$), see figure 6.6c.

6.3.4.3 RVIP

No significant findings were revealed for this task.

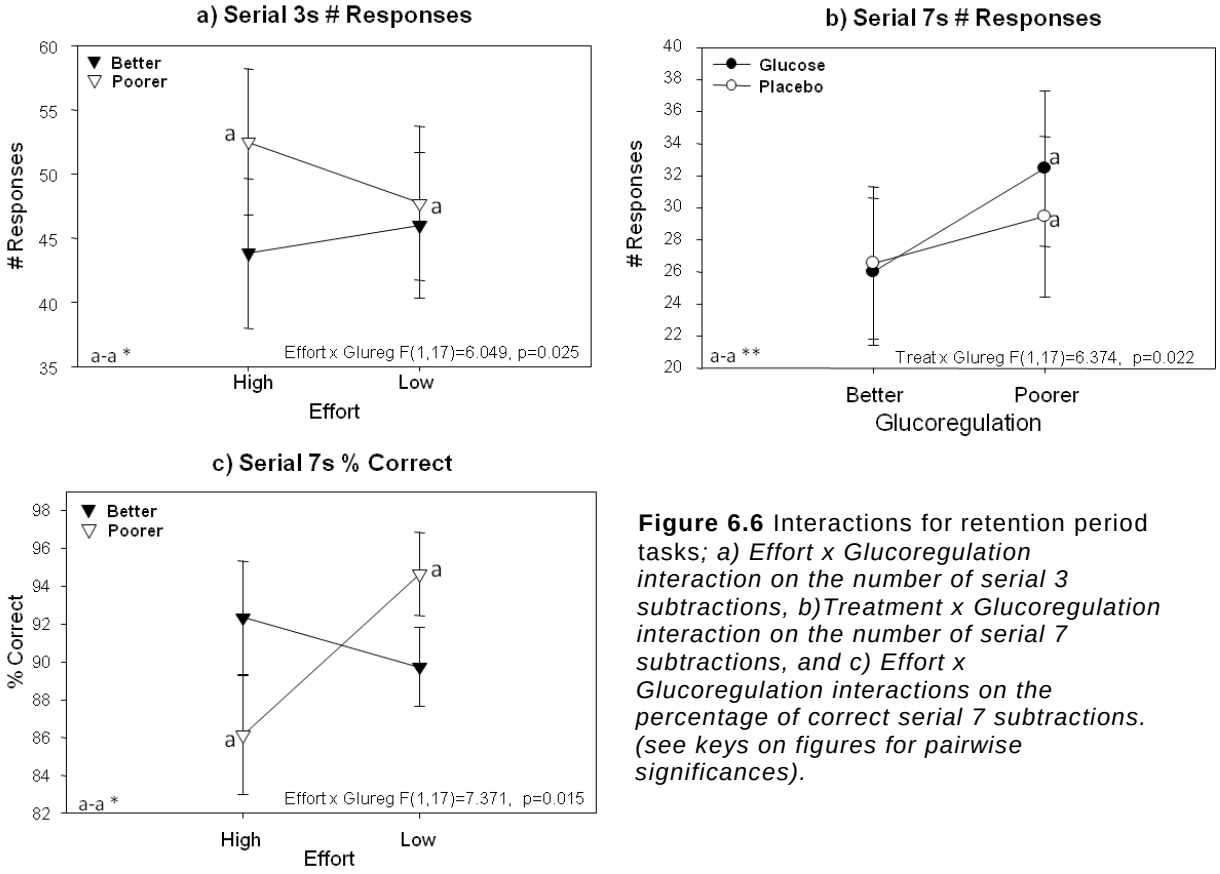


Figure 6.6 Interactions for retention period tasks*; a) Effort x Glucoregulation interaction on the number of serial 3 subtractions, b)Treatment x Glucoregulation interaction on the number of serial 7 subtractions, and c) Effort x Glucoregulation interactions on the percentage of correct serial 7 subtractions. (see keys on figures for pairwise significances).*

6.3.5 Mood and Satiety Measures

Table 6.5 below gives the means, SEM and significant effects for the mood and satiety measures taken.

6.3.5.1 Bond Lader

A main effect of treatment indicated decreased 'Calm' following glucose (F(1,18)=5.342, p=0.033, r=0.479). A significant time x glucoregulation interaction on 'Content' (F(1,18)=4.572, p=0.046, r=0.450) revealed increased contentment in poorer regulators at pre-test (t(18)=2.233, p=0.039, with decreased contentment in poorer regulators at post vs. pre test (t(18)=2.128, p=0.047), see figure 6.7a

Table 6.5. Mean change scores and SEM for each mood and satiety outcomes from the Bond Lader, VAS and SF STAI. Significant effects and interactions are indicated in the final column *(Ef = Effort, Ti = Time, Tr = Treatment, Glureg = Glucoregulation, *p<0.05, **p<0.01).*

Task	Outcome	Change	Task Effort Level	Glucoregulation Group	n=	Glucose			Placebo			Significant Effects & Interactions
						Means	±	SEM	Means	±	SEM	
SF STAI	Stress	Baseline - Pre-Test	High	Better	10	0.20	±	0.55	-0.30	±	0.63	Ef x Tr * Glureg x Ti x Tr **
				Poorer	9	0.22	±	0.55	-0.89	±	0.73	
			Low	Better	10	-0.10	±	0.28	0.40	±	0.27	
				Poorer	9	-1.00	±	0.65	0.44	±	0.88	
		Baseline - Post-Test	High	Better	10	-0.20	±	0.77	-0.60	±	1.10	
				Poorer	9	0.78	±	0.62	-0.67	±	0.87	
			Low	Better	10	-0.50	±	0.31	1.20	±	0.61	
				Poorer	9	0.56	±	0.77	0.00	±	1.03	
VAS	Hunger	Baseline - Pre-Test	High	Better	10	4.30	±	2.23	-5.00	±	3.95	Ti * Glureg x Ti x Tr *
				Poorer	10	-7.20	±	3.67	-11.10	±	1.38	
			Low	Better	10	1.50	±	3.17	1.90	±	4.77	
				Poorer	10	-11.00	±	4.16	-8.40	±	3.51	
		Baseline - Post-Test	High	Better	10	13.20	±	4.84	-0.30	±	5.14	
				Poorer	10	-9.90	±	4.72	-7.60	±	2.97	
			Low	Better	10	6.90	±	6.33	0.00	±	3.46	
				Poorer	10	-9.60	±	6.24	-1.60	±	5.80	
	Thirst	Baseline - Pre-Test	High	Better	10	-3.80	±	5.29	-5.20	±	4.89	Ti **
				Poorer	10	-12.40	±	4.79	-10.10	±	4.62	
			Low	Better	10	-6.50	±	6.32	0.70	±	6.88	
				Poorer	10	-15.80	±	7.05	-7.10	±	3.98	
		Baseline - Post-Test	High	Better	10	3.90	±	7.37	3.80	±	5.78	
				Poorer	10	-3.60	±	4.74	-2.60	±	4.78	
			Low	Better	10	-0.90	±	7.18	2.80	±	4.48	
				Poorer	10	-18.60	±	6.41	-8.60	±	3.01	
	Alert	Baseline - Pre-Test	High	Better	10	-7.20	±	6.59	4.90	±	4.34	Ef x Glureg x Ti *
				Poorer	10	-1.50	±	4.61	4.40	±	2.60	
			Low	Better	10	-1.90	±	3.17	-1.20	±	7.99	
				Poorer	10	6.40	±	5.00	0.40	±	3.75	
		Baseline - Post-Test	High	Better	10	2.60	±	2.60	9.30	±	3.09	
				Poorer	10	-1.40	±	5.35	-0.90	±	3.07	
			Low	Better	10	-3.70	±	4.86	0.10	±	8.04	
				Poorer	10	4.90	±	8.39	4.40	±	4.39	
	Stressed	Baseline - Pre-Test	High	Better	10	9.70	±	5.90	4.10	±	3.39	-
				Poorer	10	1.00	±	3.54	2.70	±	6.72	
			Low	Better	10	1.10	±	4.47	1.40	±	1.52	
				Poorer	10	0.80	±	3.55	-7.20	±	4.42	
		Baseline - Post-Test	High	Better	10	7.30	±	4.44	3.80	±	6.60	
				Poorer	10	4.00	±	4.13	7.40	±	7.49	
			Low	Better	10	1.90	±	3.56	6.30	±	3.68	
				Poorer	10	7.20	±	10.04	-1.90	±	5.30	
Bond	Alert	Baseline - Pre-Test	High	Better	10	-5.53	±	7.41	0.96	±	1.88	-
				Poorer	10	2.56	±	2.77	1.36	±	1.34	
			Low	Better	10	1.30	±	2.90	1.13	±	1.59	
				Poorer	10	1.03	±	3.85	2.60	±	1.52	
		Baseline - Post-Test	High	Better	10	2.52	±	2.68	3.69	±	4.21	
				Poorer	10	-0.14	±	3.19	-2.03	±	2.97	
			Low	Better	10	1.70	±	2.95	0.43	±	3.37	
				Poorer	10	-10.24	±	9.95	5.17	±	3.46	
	Content	Baseline - Pre-Test	High	Better	10	-1.26	±	2.47	2.40	±	2.20	Glureg x Ti *
				Poorer	10	3.02	±	2.79	-0.16	±	1.79	
			Low	Better	10	-3.76	±	2.07	-3.16	±	0.84	
				Poorer	10	2.38	±	1.97	3.20	±	2.84	
		Baseline - Post-Test	High	Better	10	-0.96	±	2.40	2.36	±	6.03	
				Poorer	10	-3.30	±	3.12	-2.54	±	3.10	
			Low	Better	10	0.68	±	1.85	-2.96	±	1.41	
				Poorer	10	-1.17	±	2.73	3.82	±	3.59	
	Calm	Baseline - Pre-Test	High	Better	10	-1.03	±	2.27	3.50	±	4.09	Tr *
				Poorer	10	-5.40	±	2.19	0.50	±	3.14	
			Low	Better	10	-1.10	±	2.34	-1.50	±	3.13	
				Poorer	10	-1.30	±	3.39	-3.60	±	2.06	
		Baseline - Post-Test	High	Better	10	-3.15	±	3.45	-0.10	±	4.40	
				Poorer	10	-9.40	±	3.59	6.70	±	5.07	
			Low	Better	10	-7.35	±	5.04	0.43	±	3.37	
				Poorer	10	-6.29	±	5.81	5.17	±	3.46	

6.3.5.2 SF STAI

For SF STAI a significant treatment x effort interaction (F(1,17)=4.692, p=0.045, r=0.465) did not reveal any significant pairwise differences, see figure 6.7b.. A time x treatment x glucoregulation interaction (F(1,17)=9.834, p=0.006, r=0.605) revealed following pairwise comparisons, poorer glucoregulators following glucose load reported increased stress from pre to post-test (t(17)=2.660, p=0.017), see figure 6.7c.

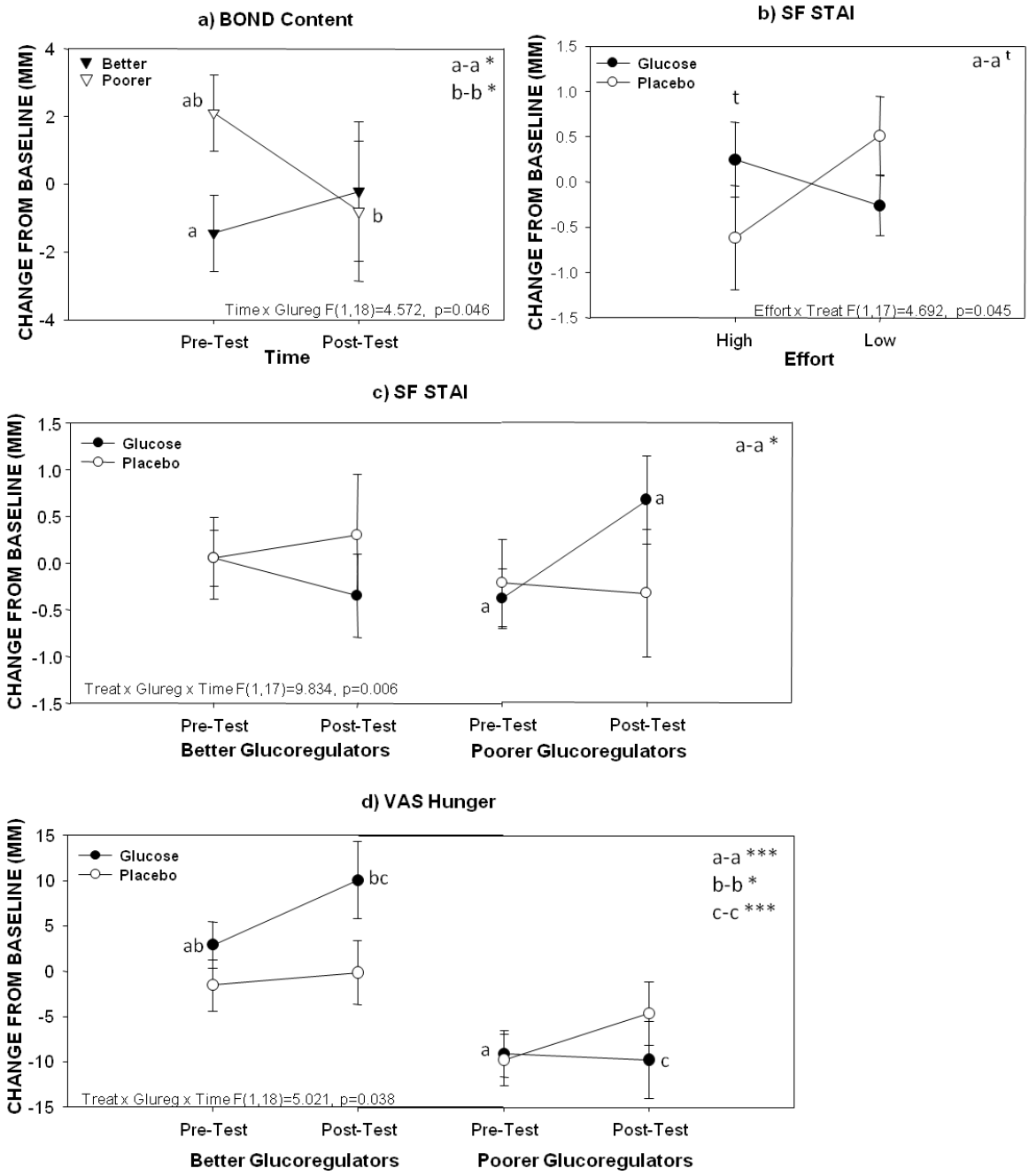


Figure 6.7 Interactions for mood and satiety measures; *a) Time x Glucoregulation interaction on Bond Content, b)Treatment x Effort interaction for SF STAI, c) Time x Treatment x Glucoregulation interaction SF STAI, and d) Time x Treatment x Glucoregulation interaction on Hunger VAS (see keys on figures for pairwise significances).*

6.3.5.3 VAS

For ‘hunger’ a 3 way time x treatment x glucoregulation interaction ($F(1,18)=5.021$, $p=0.038$, $r=0.467$), revealed several significant pairwise effects, see figure 6.7d. At pre-test ($t(18)=3.333$, $p=0.004$) and post-test ($t(18)=3.299$, $p=0.004$) better regulators were hungrier following glucose than poorer regulators. Better regulators reported increased hunger at post-test compared to pre-test following glucose ($t(18)=2.491$, $p=0.023$). Better regulators at post-test were hungrier following glucose than placebo ($t(18)=2.197$, $p=0.041$).

For ‘thirst’ there was a main effect of time, with increased thirst at post-test ($F(1,18)=8.527$, $p=0.009$, $r=0.567$).

For ‘alert’ a 3 way interaction between time, effort and glucoregulation ($F(1,18)=7.454$, $p=0.014$, $r=0.541$) did not reveal any significant pairwise differences.

6.4 Discussion

6.4.1 Summary of Main Findings

The memory blocking effect paradigm, as employed here, is a useful tool in assessing the impact of glucoregulation and potential glucose facilitation interaction with executive control, activation and suppression/inhibition of memory by installing memory blocks. Unlike chapter 5, the MBE uses orthographically similar stimuli as opposed to semantically linked stimuli. The stimuli presented during the word display phase act as either blocking (interfering) or neutral primes during a word fragment completion task.

A glucose load did not show any effect on outcomes which were subjected to interference by the initial blocking primes (e.g. intrusions and omissions), however, glucoregulatory control did appear to have considerable impact on these outcomes. Better glucoregulators were found to be slower to initiate responses. An effort by glucoregulation interaction on the number of intrusions indicated that poorer regulators were more susceptible to suffer from intrusions that better glucoregulators following low effort, although this effect was ameliorated following high effort. These findings indicate that while glucoregulatory control may mediate activation and executive control processes, a glucose load was not observed to moderate these processes.

6.4.2 Blood Glucose

Glucoregulation median splits formed two groups of regulators, whose response to the OGTT differed significantly, with the higher evoked circulatory blood glucose levels becoming apparent 30 min post ingestion for poorer regulators, with these higher levels reaching statistical significance throughout the remainder of the post-challenge period. This suggests that this grouping does allow interpretation of the findings to be discussed in terms of assessing the performance of 2 cohorts representing a better and poorer level of the glucoregulatory response spectrum. Fasting blood glucose levels did not differ between the cohorts, and presented within normal fasting range.

Statistical analysis of study day blood glucose levels did not reveal any glucoregulatory effects despite differences in blood glucose levels during the OGTT. However, several outcomes throughout the study do and these will be addressed. As expected

administering a glucose load raised circulatory glucose levels. The high effort condition decreased circulatory glucose, more markedly so following a glucose load (see figure 6.4a). This suggests that in both better and poorer regulators, increased task effort does elicit increased utilisation/processing of the increased circulatory resources, providing support for studies finding glucose facilitation effects occurring selectively in tasks with increased difficulty/mental demand (e.g. Sünram-Lea et al., 2002a). Interestingly, whilst high effort following placebo does not seem to affect the glucose response in poorer regulators, in better regulators prior to the high effort task, glucose levels do seem to increase, remaining elevated through to post test (see figure 6.4b). Participants were alerted to visits whereby they would be completing the high effort condition by the presence of a camera set up at their testing station. Whilst this effect was not significant in this study, a similar finding in chapter 3 does indicate that better regulators are better able to anticipate imminent increased demand, enabling pre-emptive provision of physiological resources to be made available. Levels of contentment, also showed better regulators to be less content at pre-test than poorer regulators, which may be due to this potential anticipation of imminent resource demand.

6.4.3 Word Fragment Completion

The primary outcomes for this chapter pertain to the word fragment completion task. Several aspects of task performance are indicative of the blocking effect; response latency, accuracy, intrusions and omissions.

Better glucoregulators demonstrated increased response latency overall, including for blocked fragments, which is the same pattern of results that has been observed in older as opposed to younger participants (Logan and Balota, 2003). This could be interpreted in a number of ways. As better regulators did not display increased overall accuracy, it is unlikely that this finding is due to a speed / accuracy trade off. It is possible that better regulators were simply slower to initiate responses, although better regulators were not slower to respond in the word recognition task, weakening this explanation. It is tenable that better regulators initiated further searching of the lexicon in order to find a suitable response to complete the fragment, with poorer regulators failing to inhibit the initially activated / retrieved response. Such an explanation is supported by inhibitory processes in ageing which may mirror that of younger poorer regulators, whereby activation remains intact but inhibition is impaired (Zacks et al., 2000, Zacks and Hasher, 1997), which may have resulted here in faster response times for the poorer regulators. Such a finding may also substantiate claims that in ageing the efficiency of the executive control is impaired

(Leynes et al., 2008), an effect which may be in part due to glucoregulatory processes and as such may contribute to these results. Unfortunately, as the response time was taken from stimuli onset until first keyed input, it cannot be ascertained from these data as to whether the first attempted response was the finally submitted response, as participants did have the option of clearing responses should they have made an error.

The most convincing evidence of glucoregulatory impact on memory blocking is seen for intrusions. In the low effort condition, poorer regulators were more susceptible to intrusions than better regulators, suggesting that greater encoding without divided attention elicits increased memory blocking in poorer but not better regulators. This finding again lends support to Zacks and Hasher's theory for increased activation of the blocking intrusion in the case, with impaired inhibition of this response type. However, the introduction of divided attention ameliorated this effect in poorer regulators, with fewer intrusions displayed, supporting the claim that divided attention does eliminate/ significantly decrease MBE, although only in poorer glucoregulators. This pattern was not found for better regulators, which suggests that better regulators (both in high and low effort conditions) are better able to overcome memory blocks, whereas poorer regulators susceptibility to the blocks is greater, with susceptibility diminished (although not to the extent of better regulators) in divided attention. Previous literature has shown that divided attention can eliminate the memory blocking effect (Kinoshita and Towgood, 2001). However, to date the literature has not addressed the potential glucoregulatory implications on performance within this paradigm. This chapter furthers existing knowledge and use of this paradigm, by providing evidence that dividing attention affects poorer regulators to a greater degree. No effect of treatment was detected here, but as glucose levels were seen to be decreased by high effort, this factor should not be ignored, as it would seem that memory blocking is greatest in poorer regulators following low effort, who concurrently will have increased circulatory blood glucose levels throughout the task.

Conversely, increased intrusions may be seen as facilitation, which in poorer regulators may be in part attributed to increased blood glucose. Increased encoding and subsequent blocking by the initial blocking prime would indicate increased memory efficiency in poorer regulators, who are responding faster to give recently retrieved and environmentally relevant responses. Whilst in this paradigm such responses are incorrect, generally speaking such a response would be beneficial to an individual, as responses retrieved quicker, with greater suppression and inhibition of similar items would streamline memory processes. Such a streamlining of response may be interpreted as greater memory efficiency, although perhaps at the expense of accuracy.

These findings suggest that poorer regulators are less able to overcome inhibition/suppression of orthographically similar items, which results in decreased searching of the lexicon, faster responses and increased intrusions. Seemingly the manipulation of dividing attention at encoding does not affect better glucoregulators susceptibility to intrusions, which suggests that better regulators may be performing optimally to overcome blocking effects. This is perhaps why blocking is not diminished by dividing attention.

No treatment effects were found with regards to the number of, or reaction time to give, an intrusion or omission response. This in conjunction with the effort x glucoregulation effect that was found, suggest that increasing circulatory glucose and hence the availability of fuel to the brain, throughout this task, is not affecting performance for these specific outcomes. When filler fragment completions are considered, treatment type does appear to be affecting performance.

6.4.4 Word Recognition

Whilst the recognition portion of this task is confounded (with blocking items intentionally accessed during the fragment task and therefore potentially more accessible), no glucoregulatory effects were found on recognition performance, with fewer correct recognitions following high than low effort (also found for blocked stimuli). This suggests that whilst high effort may be decreasing encoding and rehearsal, this is not differentially affecting better and poorer regulators. Higher circulatory glucose levels following low effort may also be contributing to increased recognition performance.

6.4.5 Retention Period Tasks

The retention period tasks in this chapter revealed slightly different findings to those reported in chapter 5. This chapter saw only poorer glucoregulators making more serial 3 subtractions following high effort, as opposed to main effort effect seen in chapter 5. A treatment x glucoregulation interaction on the number of serial 7 subtractions revealed glucose facilitation in only poorer glucoregulators, who made more responses following glucose than placebo. The high effort manipulation reduced the accuracy of serial 7 subtractions in poorer glucoregulators following high effort. Completion of the RVIP task did not reveal any significant effect or interactions.

There are several factors which may account for the differences in performance on these tasks between chapter 5 and 6. In chapter 5, there was a delay between completing the dual task and the retention period tasks, whilst the relatively easy repeated retrieval task was completed. In chapter 6 however, the retention period tasks were completed immediately after the word display with dual task.

6.4.6 Mood and Satiety Scales

It is reasonable to suggest that the high effort component of this task would increase perceived effortfulness and stress encountered. However, no effects were found on the effortfulness VAS (completed at the end of the visit) or Stress VAS (completed at Baseline, Pre and post test). The SF STAI again showed no effort effects. This could indicate that the effort manipulation did not impact upon participant's perceived exertion (both anticipatory to task completion and following the tasks). However, since measures were taken before and around 20 minutes post high effort task, it is likely that participants had recovered from any such effects, with the measurements therefore missing these points. An alternate view is that the fragment task in itself was a difficult task to perform, with participants anecdotally describing their frustration. This more recent fragment task may have superseded perceptions of the dual task, and as it was completed in both high and low effort, may account for the lack of effort manipulation effect on perceived effort and stress.

Self reported hunger (see figure 6.7d), shows differential response patterns emerge from better and poorer regulators following consumption of the caloric glucose drink versus the placebo, with better regulators reporting to be hungrier at both pre and post test than poorer regulators. Literature which has assessed /reviewed appetitive states following consumption of non-nutritive compounds in relation to nutritive compounds, has found conflicting evidence of increased hunger or no effect following saccharine (and similar non-nutritive compounds), but decreased hunger following a caloric load (Rolls, 1991, Canty and Chan, 1991, Mattes and Popkin, 2009, Renwick, 1994, Vermunt et al., 2003, Rogers and Blundell, 1989). These studies have not, however, assessed the interplay between appetitive states following nutritive and non-nutritive loads in the context of differing glucoregulatory responses (nor cognition), which may account for the limited support and refutation of such findings in this chapter. In better regulators hunger remains constant across time following placebo, whereas in poorer regulators, hunger is decreased at pre-test (although not significantly). Strikingly, the consumption of glucose actually increased reported hunger in better regulators, but decreased hunger in poorer

regulators, the latter running counter to published literature (Renwick, 1994, Rogers and Blundell, 1989, Vermunt et al., 2003). This finding infers that an individual's level of glucoregulation has a key role to play in the perception of hunger and subsequent energy intake, which should not be overlooked when investigating appetitive states. The differential finding may (at least in part) be explained by poorer regulators decreased ability to effectively process the consumed treatment. The lower levels of hunger reported by poorer regulators may be influenced by increased reliability on alternative regulation properties to better regulators. Better regulators may be able to more accurately sense the calorific content of the treatment in the intestinal tract, with more efficient accurate signalling and appropriate responses generated by the endocrine system (see section 1.2 for details of digestion and subsequent metabolism) and subsequent neuronal processing. Poorer regulators in lieu of this may be suffering from over reliance on alternative systems e.g. gastric emptying to interpret satiation. As the glucose drink has increased viscosity and empties more slowly (Little et al., 2009). This may explain why poorer regulators hunger levels do not increase at post test following glucose, but better regulators do. Suggestions of differing responses in the functioning of endocrine systems (not solely those explicitly linked to glucose metabolism, for example ghrelin and leptin) between better and poorer glucoregulators, adds weight to underlying physiological effects which may be impacting on cognitive functioning, differentially affecting performance. Ghrelin has been shown to modulate hippocampal function and memory function in rats (Atcha et al., 2009, Diano et al., 2006), an effect which may be exerting an influence on memory performance here.

6.4.7 Conclusion

In conclusion, using a MBE paradigm this chapter has explored the potential glucose and glucoregulatory impact of various outcomes within the word fragment completion phase. A glucose load did not show any statistical effect on outcomes which were subjected to interference by the initial blocking primes, however, glucoregulatory control did appear to have considerable impact on these outcomes. Poorer regulators were prone to more intrusions than better regulators, mirroring findings from age and MBE studies and suggesting that age-related impairments in glucose regulation may contribute to this phenomenon. Interestingly response latency was slower for better regulators, which may be considered a decrement. This chapter, however, argues that slower response times may actually have been indicative of greater searching of the lexicon by better regulators and/or of greater executive control being exhibited by better regulators, with more effective management of activation and inhibition of responses throughout. The

incorporation of a dividing attention dual task at encoding also generated some interesting interactions with glucoregulation, with carryover effects from the increased demand seemingly impacting later, non related tasks (e.g. serial 7s subtraction). An interaction between time, glucoregulation and treatment, suggests that differing hunger responses to treatments, may be impacting on task performance.

CHAPTER 7. DISCUSSION

7.1 Summary of the Objectives of the Thesis

The aim of this thesis was to address the influence of a glucose and glucoregulation on different aspects of verbal declarative memory. Verbal declarative memory is believed to be the aspect of memory that most reliably shows beneficial effects of glucose (Messier, 2004). Whilst several studies have reported glucose facilitation of declarative memory in healthy young adults (Benton et al., 1994, Foster et al., 1998, Meikle et al., 2005, Sünram-Lea et al., 2001, Sünram-Lea et al., 2008), a considerable body of research has observed no such facilitation (Brandt et al., 2006, Ford et al., 2002a, Green et al., 2001, Kennedy and Scholey, 2000, Scholey et al., 2001, Sünram-Lea et al., 2002a).

A glucose load has been shown to influence the memory performance of different populations, often in opposite directions. For example, conflicting findings have been reported when considering the influence of glucose upon individuals with varying glucoregulatory control. Better glucoregulators have been found to demonstrate more pronounced facilitation in response to a glucose load (Craft et al., 1994, Meikle et al., 2004, Messier et al., 1997), but equally so have poorer glucoregulators (Awad et al., 2002, Messier et al., 1999). In light of the contradictory evidence to date, this thesis aimed to investigate the effect of glucoregulatory control on memory, in response to a glucose load within healthy young adults who had not been diagnosed with any metabolic disorders.

The paradigms used to date within the glucose literature to assess declarative memory have tended to use standard word display with recall and /or recognition phases. Chapters 3 - 6 within this thesis employ novel memory paradigms adapted from the cognitive sciences literature to investigate the effect of glucose and glucoregulation on different phases of declarative memory. The paradigms used make particular reference to an individual's level of forgetting as both an advantageous and as a disadvantageous response, depending on whether forgetting was intended or not. This has enabled inferences to be drawn with regards the efficiency of memory and potential interaction with glucose facilitation and levels of glucoregulatory control.

A further manipulation employed in chapters 3 – 6 was the inclusion of a high effort / dual task. In young adults whose performance is likely to be nearing optimal levels, the beneficial effects of glucose is seemingly more detectable during cognitively demanding tasks (Foster et al., 1998, Sünram-Lea et al., 2002a, Sünram-Lea et al., 2001, Sünram-

Lea et al., 2002b, Sünram-Lea et al., 2004). The population selected for chapters 3-6 of this thesis were young adults, primarily because even those presenting with poorer glucoregulatory control were less likely to have conditions such as cerebrovascular damage, as seen in older individuals with a history of impaired glucoregulatory control (Lamport et al., 2009). Consequently by employing a dual task and increasing the demand level of the paradigms, it was hoped that the threshold of susceptibility to glucose may be lowered and any treatment effects that were not detectable during lesser demanding tasks, would become evident.

No studies published to date have conducted a dose ranging study of glucose and cognition in children, with limited research having administered a glucose drink treatment to this population. Young children's brains have approximately double the metabolic rate of that found in adults (Chugani, 1998, Kalhan and Kilic, 1999). By investigating the effects of glucose in this population, this thesis aimed to a) generate new knowledge which will enlighten this under investigated population and b) potentially provide insight into the possible mechanisms by which glucose may be acting to influence cognition but specifically memory. Addressing this gap in the existing literature formed the starting point of this thesis (chapter 2).

Below is a brief summary of the aims that this thesis aimed to address

- Research published to date has inferred declarative memory is the domain most susceptible to the glucose facilitation effect. However, the standard paradigms used cannot infer specifically which aspects of declarative memory may be being targeted by / susceptible to the glucose enhancement effect. With particular reference to memory efficiency and in particular forgetting, this thesis aimed to employ novel paradigms from the cognitive sciences literature to further explore this issue.

- To further the existing knowledge on the influence of an individual's level of glucoregulatory control on both declarative memory and any potential interaction with glucose facilitation. By investigating young healthy adults, who are unlikely to be affected by confounding health damage related to poorer glucoregulation (e.g. cerebrovascular damage), any glucoregulatory interaction found should be more confidently attributed to the effects of glucoregulatory control.

- Through manipulating circulatory blood glucose levels and task demand (in conjunction with measures of glucoregulatory control), this thesis aimed to further elucidate the mechanisms by which glucose may be enhancing memory.

- Additionally, a distinct gap in present knowledge pertaining to the influence of glucose administration in children was addressed. Using a wide range of tasks an overview was sought as to how various glucose doses may influence cognition in children.

In order to achieve the aims above, the following studies were conducted:

- Chapter 2 – A dose-ranging response study in 10 year old children to investigate the potential susceptibility of a range of cognitive tasks to glucose facilitation.

- Chapter 3 – An investigation of the impact of glucose and glucoregulation on recollection and familiarity recognition.

- Chapter 4 – An evaluation of the impact of glucoregulatory control and glucose facilitating effects on encoding efficiency, via the item method directed forgetting paradigm.

- Chapter 5 – An investigation of glucoregulatory and glucose facilitation effects on inhibition via the retrieval induced forgetting paradigm.

- Chapter 6 – An evaluation of glucoregulation and facilitation effects of glucose on the memory blocking effect.

7.2 The effects of Glucose and Glucoregulation on Memory

While the studies within this thesis (chapters 3-6) significantly raised circulatory glucose levels through ingestion of a glucose load (circulating blood glucose was not measured or analysed in chapter 2 due to ethical considerations, but may be assumed to have been elevated during the 30 min post dose test session following 20 g and 40 g glucose treatments), relatively few treatment effects were observed on memory. The influence of glucose, effort and glucoregulatory control (where applicable) on memory outcomes are discussed for each chapter in turn here.

Chapters 3-6 assessed healthy young adults, who have previously been shown to be susceptible to declarative memory enhancements following glucose administration. The unique nature of the paradigms utilised in chapters 3-6, the fact that they have not been used before within a glucose enhancement context and the memory manipulations

employed within them, means that the outcome measures (such as word recall and recognition) are not directly comparable between the chapters. Subsequently the chapters and their implications are considered in turn, with more general conclusions with regards to the specific phases of declarative memory and their susceptibility to glucose administration drawn later in this chapter.

7.2.1 The effects of Glucose on Memory in Children

In chapter 2, it was hypothesised that children may be as susceptible, if not more so, to memory facilitation through glucose administration as young adults, due to the high rate of glucose metabolism in the brain of this age group (Chugani, 1998, Kalhan and Kilic, 1999). However, gaps in existing knowledge left this question open to speculation. Following analysis, no glucose effects or glucose by time interactions were observed on any outcome assessing memory (word recall: immediate and delayed, verbal fluency), for any of the treatments administered (0 g, 20 g or 40 g). This may be interpreted in a number of ways. Firstly, 10 year old children may not be susceptible to any memory enhancing effects following raised circulatory glucose levels having consumed 20 g or 40 g of glucose. This finding replicates previous literature, which using similar methodology also failed to elicit memory enhancement following a 38.3 g glucose drink (Wesnes et al., 2003). However, Wesnes et al. (2003) reported impairments in word recall following glucose when compared to a no treatment condition. Chapter 2 of this thesis however, found no recall differences following either glucose dose in comparison to a saccharine placebo. The differences in these findings may be attributable to the age ranges tested. Wesnes et al. (2003) tested a range of 9-16 year olds, whereas chapter 2 solely tested 10 year olds. As the metabolic rate of the brain declines dramatically from the age of 10 – 16 years (Chugani, 1998), it may be that the older children tested in Wesnes et al.'s study were more affected by the circulatory glucose nadir found following circulatory glucose levels return to baseline. Such a drop below fasting levels of circulatory glucose would not have been a factor after receiving no treatment, potentially accounting for the impairments observed following glucose administration.

It is conceivable that the glucose doses which were administered here were not sufficiently high as to enable facilitation. A maximum dose of 40 g of glucose was administered, although previous studies have found (in healthy adult populations) doses of 50 g (e.g. Messier et al., 1999) and 60 g (e.g. Owen et al., 2010) of glucose to be effective in facilitating memory performance. The assumed good glucoregulatory control within this population may have allowed circulating glucose levels to be rapidly returned to

baseline levels, meaning that additional glucose was not available in order to facilitate performance.

A further account for the lack of significant effects may be that the children were operating at a ceiling level of performance, with no further margin for facilitation remaining to be influenced by a glucose load. Whilst plausible, it seems somewhat unlikely that this was the case for the verbal fluency task as time effects were observed here (these were not discussed in text but were indicated in the outcome tables). No such time effects were seen during the word recall task (Immediate or delayed). This indicated that potential ceiling effects for this outcome should be given consideration however, it should also be noted that the children did not achieve maximum scores for this task.

The only cognitive task outcome to display a treatment effect was the arrow flankers task. This task is a challenging forced choice task, with flanking symbols interfering to alter the decision difficulty of the stimuli presented (being congruent, incongruent, non-interfering etc). Surprisingly performance on this task was impaired following consumption of a 20 g glucose load, with more incorrect responses given when compared to placebo and 40 g glucose. One potential issue discussed within chapter 2 is the influence of the hypertonic nature of the drink leading to a dehydrating effect. This introduces the possibility that the impairments observed following 20 g were the result of dehydration. These dehydration induced deficits may have been somewhat overcome by the additional energy provision following 40 g in spite of the increase hyper tonicity (see section 7.6.2.1 for further discussion). However, no such effects were found on memory performance in children.

The differences observed between Wesnes et al. (2003) and chapter 2 may lie in hydration status differences. There were sizeable difference in the volume of the drinks administered (150 ml in chapter 2 as opposed to 330 ml in Wesnes et al. (2003)), which may have allowed for alternative effects e.g. hydration status, volume sensing, satiety signalling to influence memory (this issue is discussed in more depth in section 7.6.2).

This population is of interest due to the high metabolic rate of the brain in this age group. In conjunction with this, (healthy) children present with excellent glucoregulatory control. It may be that the failure to elicit any memory enhancing effects in this population can be attributed to this efficient glucoregulatory control. Excellent glucoregulatory control may be effective at preventing any memory enhancement or impairments following a supplementary glucose load, through the accurate maintenance of optimum levels. This suggestion does warrant further exploration, as previous research in adolescents has found glucose facilitation in better glucoregulators (Smith and Foster, 2008). However,

conflicting evidence in adults has shown both better and poorer glucoregulators to be susceptible to glucose facilitation (see section 1.3.4). Glucoregulatory control does decline over the course of the day (Owens et al., 1996, Van Cauter et al., 1997), which may account for the somewhat more positive findings for glucose facilitation in children studies which have tested later in the day (Benton and Stevens, 2008). However, in adults Sünram-Lea et al. (2001) did not find differential glucose facilitation regardless of whether testing was completed in the morning or afternoon.

As glucose facilitation is more readily observed in demanding memory tasks in young adults (see section 1.3.5), one potential avenue for further research in children would be to employ dual task / divided attention techniques with memory tasks in glucose studies following glucose ingestion. This would enable the findings from children to be more readily compared with the memory studies conducted in adult populations. This manipulation has previously been successfully employed in an older cohort of adolescents, during verbal declarative memory tasks (Smith and Foster, 2008). Enhancements in verbal declarative memory were observed by glucose in comparison to placebo subsequent to divided attention during encoding.

Measurements of circulatory blood glucose in conjunction with administration of an OGTT would also enable further insight into the specific glucoregulatory control of the tested cohort. In adolescents, there is tentative evidence that better glucoregulators (as determined by AUC during a glucose test visit) benefit from the glucose facilitation of verbal declarative memory (Smith and Foster, 2008). While blood glucose measurements were deemed too invasive for the purposes of this research, advances in continuous and non-invasive measuring equipment allowing reliable measures of glucose levels could be effectively utilised in future research (although many of these do require an initial fingerprick measure for calibration purposes). A further consideration is that only healthy children were recruited into this study, with the BMI for all children falling within the healthy range as determined by Cole et al. (2000). The recruitment of a greater range of children exhibiting varying levels of glucoregulatory control would enable greater insight into the potential mechanisms which may be acting to protect memory in this population.

Although there are several methodological issues (outlined above) that may be obscuring any potentially observable effects, with several conflicting findings reported in the literature published to date, the evidence from this study suggests that healthy children aged 10 years old are not susceptible to any performance changes in declarative memory following 0 g, 20 g or 40 g of glucose.

7.2.2 The Impact of Glucose and Glucoregulation on Recollection and Familiarity Recognition.

Chapter 3 assessed the potential impact of glucose and glucoregulation on recollection and familiarity processes during a recognition task (following word display and a filled retention period). This paradigm has been utilised within the glucose literature previously, however, contradictory findings have been reported (Smith et al., 2009b, Sünram-Lea et al., 2008). The remember / know paradigm was used to investigate whether the glucose facilitation effect is preferentially targeting functions associated with hippocampal activity ('domain') or a more global facilitation during highly demanding cognitive processes ('demand').

It was hypothesised that should glucose facilitation preferentially target the hippocampal domain, facilitation of recollection recognition processes would be observed with no effects observed on familiarity recognition. The results from chapter 3 did not indicate any such advantage of recollection recognition following glucose administration, nor did glucose elicit increased recognition accuracy (even following increased demand). These findings contradict those published by Sünram-Lea et al. (2008), who reported glucose facilitation of recollection recognition in a between subjects design in healthy young adults. The results do concur with those of Smith et al. (2009b), who found no advantage of recollection over familiarity recognition in adolescents. Smith et al. (2009b) did however, observe an overall glucose facilitation of accuracy, which was not replicated in chapter 3.

Interestingly the speed of recognitions was found to show glucoregulation x treatment x effort interactions. Whilst the interactions did not reveal an unequivocal effect patterns, they did indicate that better and poorer glucoregulators responded differently to the glucose load under the differing demand manipulations. Better regulators seemingly benefited from faster correct response times following glucose, but only following the low demand task. Although Smith et al. (2009b) did not quantify glucoregulatory control, glucose effects on response times in adolescents (assumed to be good glucoregulators) were speeded following the consumption of glucose as opposed to placebo, in line with the response time effects observed in better glucoregulators in chapter 3.

Since no glucoregulatory effects were observed on the recollection or familiarity recognition accuracy, this may be interpreted to suggest that the ageing deficiencies seen in recollection recognition (Light et al., 2000, Park et al., 2010, Prull et al., 2006,

Yonelinas, 2002), are not attributable to declining glucoregulatory control. Although equally, the reaction time effects do hint that whilst recognition accuracy may not be vulnerable during the early phases of glucoregulatory decline, impairments may develop as a consequence of prolonged poor glucoregulatory control and the associated damage. The findings reported in chapter 3 also indicate that the differing endocrine responses (as indicated by varying degrees of glucoregulatory control) such as insulin, are not mediating recognition accuracy or type, at least not for word stimuli presented visually, or to such an extent that any effects were detectable here. It may be however, that recognition effects / impairments may develop with accumulative damage (e.g. cerebral-vascular damage, increased insulin resistance) over time. This provides a rationale for employing this paradigm across a range of populations, with varying levels and lengths of exposure to the sequelae of sub-optimal glucoregulatory control. As noted in chapter 3, the method of determining glucoregulatory control was not as rigorous as the OGTT employed in other chapters and was somewhat compromised by both the dose of glucose and also the use of blood glucose response during a testing session. Although this is not unusual in this field, caution should be applied to these findings.

The variability in the findings reported in chapter 3 and other glucose literature investigating recollection and familiarity recognition (Smith et al., 2009b, Sünram-Lea et al., 2008), highlights the contradictory nature of glucose research to date. It should be noted that certain methodological differences between the studies may be responsible for the varying results reported in these recognition studies (E.g. the inclusion of a secondary task in Smith et al. (2009b) but not Sünram-Lea et al. (2008)). Perhaps though, the most salient methodological issue is the mode of stimuli presentation. Aggleton and Brown (1999) suggest that the modality of stimuli presentation (verbal vs. non-verbal) leads to distinct activation of the hippocampus. The left hippocampus is believed to mediate verbal learning whereas the right hippocampal region mediates non-verbal learning. Consequently the glucose facilitation following auditory stimuli presentation as employed by Sünram-Lea et al. (2008), may not be targeting the same specific neuroanatomical loci, as the facilitation reported following visually presented stimuli as utilised by Smith et al. (2009b). More generally, should glucose facilitation be acting differentially on separate sensory modalities, care should be taken when drawing comparisons across the literature in which presentation of stimuli is not uniform.

7.2.3 The impact of Glucose and Glucoregulation on Encoding Efficiency through the Directed Forgetting paradigm

Chapter 4 assessed the impact of glucose administration and glucoregulatory control on encoding efficiency using the item method of the directed forgetting (DF) paradigm. This paradigm has not (to the authors knowledge) been employed previously to investigate any nutritional or pharmaceutical interventions on encoding efficiency. In older adults deficits in memory encoding are common, which are believed to be due (at least in part) to deficient inhibitory mechanisms (Hasher et al., 1989). Such impairments subsequently manifest as decreased directed forgetting (decreased forgetting of 'to be forgotten' [TBF] items) (Dulaney et al., 2004, Sego et al., 2006, Zacks et al., 1996). As glucoregulatory control also declines in older adults (Awad et al., 2004, Messier et al., 1999, Messier and Gagnon, 1996), it was hypothesised that poorer glucoregulatory control may be mediating the encoding deficits observed in older adults. It may then have been expected that poorer glucoregulators would display decreased levels of DF, but that these individuals would also be more susceptible than better glucoregulators to glucose enhancement effects.

The DF paradigm was successfully employed, with fewer TBF items recalled than 'to be remembered' (TBR) items, although the accuracy effects observed were not straightforward. Glucose did not mediate DF at immediate or delayed recall, with no effects observed on the proportion of correctly recalled items. This finding indicated that encoding efficiency was not enhanced by glucose in chapter 4. However, some interesting effects regarding the errors made during immediate free recall, suggest that the lack of glucose facilitation on the traditional DF outcomes may not be fully representative of the effects elicited. Increased errors at immediate recall were generated by participants following; glucose with high effort, better glucoregulators with glucose and by better glucoregulators completing the high effort manipulation (although no treatment x effort x glucoregulation interaction was observed). Generally, an increased error rate is perceived as being disadvantageous to the participant (much as forgetting is often interpreted as a cognitive failure), although this may not be the case. The increased immediate recall errors made may reflect several adaptive processes. One interpretation presented in chapter 4, suggests that better glucoregulators may be attempting to retrieve items that were designated as to be forgotten, however, efficient cessation of encoding of TBF items prevented accurate recall. If this explanation proved to be correct, then this would indicate that glucose and good glucoregulatory control do improve encoding efficiency, particularly during demanding tasks. Alternatively the errors may represent participant's attempts to retrieve TBR items whose encoding was not fully elaborated due

to the increased cognitive demand induced by the dual task. More tenacious attempts to retrieve such information (whilst admittedly resulting in increased errors), may indicate greater elaborate encoding and potentially an increased capacity / protection from the deficits induced through the highly demanding task, both by glucose and in better glucoregulators. These findings purporting to errors may be spurious, however, they may indicate encoding efficiency is susceptible to mediation by glucose and glucoregulation.

The tentative evidence from chapter 4 suggests that encoding may be targeted by glucose administration and be mediated by glucoregulatory control, with better glucoregulators seemingly more prone to glucose facilitation of encoding efficiency. Brain imaging (using fMRI) concurrently recorded during this paradigm has previously indicated that increased activation in the hippocampus and superior frontal gyrus is present during intentional forgetting (Wylie et al., 2008). Additionally increased positivity in ERPs following a forget cue in the frontal and prefrontal areas, suggests that frontal and prefrontal activity serves to limit encoding (Hsieh et al., 2009, Paz-Caballero et al., 2004). Subsequently it is possible that any glucose effects may be targeting the frontal and prefrontal areas of the brain, in addition to the hippocampus. Whilst firm assertions may not be drawn, the application of brain imaging would further elucidate the specific effects observed here, in particular allowing further insight into brain areas / circuitry and mechanisms responsible for the increased errors generated.

7.2.4 The impact of Glucose and Glucoregulation on Retrieval Induced Inhibition during the Retrieval Induced Forgetting paradigm

Whilst chapter 4 tentatively suggested that encoding efficiency may by susceptible to enhancements by glucose, particularly in better glucoregulators, the role of retrieval inhibition processes were unclear. Failure to inhibit the retrieval of competing yet inappropriate memories decreases the effective retrieval of appropriate information leading to memory failures. Chapter 5 specifically examined the role of glucose and glucoregulation on retrieval inhibition utilising the retrieval induced forgetting (RIF) paradigm. It was postulated that poorer glucoregulators may exhibit decrements in inhibitory processes, relative to better regulators and may also be more susceptible to any glucose facilitation.

The findings revealed no evidence for glucose facilitation of inhibitory or retrieval processes during the primary word recall outcome for RIF. However, limited evidence did indicate that glucoregulatory control may be modulating successful retrieval inhibition.

Better glucoregulators displayed a greater magnitude of RIF in comparison to poorer glucoregulators, regardless of the effort manipulation. This finding potentially indicates that decreased glucoregulatory control may be decreasing efficient deployment of cognitive resources to allow effective inhibition of competing semantically related items from the lexicon.

Greater inhibition was also observed following the high effort manipulation across glucoregulatory levels. As the retrieval inhibition phase of this study was completed immediately following the high demand task, it was postulated that a 'carry over' effect resulting from the greater cognitive demand elicited the improvements in retrieval inhibition. Several mechanisms may be accountable for this effect. The increased cognitive demand of the high effort manipulation should have induced greater metabolism within the brain, with elevated metabolic resources subsequently being available to enable effective retrieval inhibition. Increased metabolic resources and subsequent metabolism provide acetyl CoA, the precursor for the synthesis of the neurotransmitter acetylcholine. Greater synthesis of acetylcholine is a notable potential mechanism through which glucose facilitation may be acting (Messier, 2004). Pharmacological interventions have previously investigated the cholinergic effects of scopolamine and nicotine on RIF (Edginton and Rusted, 2003, Rusted and Alvares, 2008). The effects observed in chapter 5 closely resemble those observed by the cholinergic agonist nicotine, lending support to this as a potential mechanism accounting for the increased RIF here.

Alternatively since glucoregulatory control appears to mediate this aspect of memory, glucoregulatory endocrine responses may be influencing retrieval inhibition. For example insulin may be acting on the hippocampus (Hoyer, 1996, Hoyer, 2003) (see section 1.4). As effort manipulations immediately prior to the retrieval inhibition phase of the paradigm influence the magnitude of the inhibition, it is also plausible that the adrenergic mechanism (see section 1.4) may also be acting to moderate inhibition efficiency.

7.2.5 The impact of Glucose and Glucoregulation on Retrieval Blocking during the Memory Blocking Effect paradigm

The inhibition of semantically related stimuli observed in chapter 5, suggests that this aspect of inhibition is not susceptible to mediation through administration of a glucose load. There was however, evidence that this is one aspect of memory on which better and poorer glucoregulators performance differs, with increased inhibition displayed in better glucoregulators. The influence of glucose and glucoregulation on retrieval

processes was further examined in chapter 6 using the MBE paradigm, whereby semantic / categorical links between the items are not required.

Based on the findings during the RIF paradigm, it was again postulated that poorer regulators would show reduced inhibition in comparison to better glucoregulators. Poorer glucoregulators actually demonstrated greater inhibition than better glucoregulators, giving greater numbers of intrusion responses during the fragment completion task. This indicated poorer regulators displayed an increased blocking effect and also a decreased ability to overcome the inhibition of the competing stimuli from retrieval. Better glucoregulators seemed to spend more time on task, prior to attempting to give a response (observed through prolonged initial response times). This was interpreted as a greater ability to continue searching the lexicon, overcoming initial suppression / inhibition during the fragment completion task. Such a finding indicates that poorer glucoregulators may suffer from decrements in executive control relative to better glucoregulators.
The findings in chapter 6, closely resemble those found in MBE ageing studies (Logan and Balota, 2003). The performance of poorer glucoregulators was reminiscent of that seen in older adults completing this paradigm, with increased intrusions displayed in comparison to better glucoregulators. Subsequently the blocking effect appears to be greater in poorer glucoregulators (as also seen in older adults), who appear to be encountering difficulties overcoming the initial activation. However, inhibitory processes are not seemingly affected in the MBE paradigm whereby the stimuli are semantically unrelated but orthographically similar (also observed in older adults). This is in contrast to chapter 5, which reported poorer glucoregulators showing decrements in inhibiting semantically related stimuli. The MBE results were interpreted to suggest that poor glucoregulatory control seems to be linked to a reduced ability to overcome the activation of a lexical competitor when attempting to retrieve a target word, through diminished executive control. A body of research investigating inhibitory memory processes in ageing does suggest that ageing presents with preserved activation but impaired inhibitory processes (Light et al., 2002, Zacks and Hasher, 1997, Zacks et al., 2000). Such inhibition deficits lead to “an elevated sensitivity to potential sources of interference, both at encoding and retrieval” (Zacks et al., 2000). Declining glucoregulation is a key feature of ageing and as such similar MBE effects may be observed not only in the elderly but also in poorer regulators. The similarity between the performances observed in poorer glucoregulators in chapter 6 and that of older adults on this paradigm (Logan and Balota, 2003), indicate that declining glucoregulatory control in older adults may be a factor influencing their performance on this paradigm.

Divided attention has previously been shown to eliminate the MBE effect (Kinoshita and Towgood, 2001), although previous research has not examined the role of glucoregulation. Chapter 6 furthers this work, and suggests that different populations may have varied responses to a high effort manipulation. Such differences are highlighted by those observed between better and poorer glucoregulators responses to a divided attention manipulation. The increased blocking (in the form of intrusions) was ameliorated by the high effort manipulation in poorer glucoregulators; however, the effort manipulation did not influence performance of better glucoregulators. In section 7.2.4 it was postulated that the high effort task may have had a 'carry-over' effect, subsequently facilitating inhibition processes. This account may also go some way to explain why the MBE observed in poorer glucoregulators, more closely reflects that only observed in better glucoregulators following the high effort manipulation.

As per chapter 5, no treatment effects (main or interactions) were observed on the MBE paradigm. This suggests that inhibition processes and executive control processes employed during this paradigm are not mediated by administration of a glucose load. The MBE paradigm also indicated executive control differences in different glucoregulator groups.

These findings have a number of implications, firstly that even in 'healthy young adults' those with poorer glucoregulation may already be affected by cognitive deficits, despite falling within the normal range. Differences observed display greater inhibition which (under everyday circumstances) would facilitate more efficient retrieval of recent stimuli / events from memory. However, in the MBE paradigm, such items intrude upon retrieval and prevent further searching of the lexicon, in order to produce a more appropriate response.

7.2.6 Summary of Memory Effects

The research presented in this thesis, found very limited evidence of glucose facilitation of memory. In chapter 2, a range of glucose doses did not mediate memory performance in 10 year old children. Several potential factors which may have obscured any glucose facilitation were identified (hyper tonicity of the drink, time of day effects etc), although these findings may simply indicate that the population tested were already function at ceiling levels for memory processes, with additional availability of glucose simply being surplus to requirements and subsequently unable to facilitate performance.

In chapter 3, no evidence was found to support previous research that glucose differentially facilitates recollection / familiarity recognition, or overall recognition accuracy. However, the findings did suggest that better glucoregulators benefited from speeded recognition response times following a glucose load in better glucoregulators following low effort.

Tentative evidence from the DF paradigm (chapter 4) suggests that glucose may target encoding processes, allowing greater control over the cessation of elaborate encoding of irrelevant information. The influence of glucose was more pronounced during a high demand manipulation, with better but not poorer glucoregulators exhibiting beneficial effects following glucose. This supports previous findings in which individuals with better glucoregulation have been shown to be more susceptible to glucose facilitation, in older (Craft et al., 1994, Meikle et al., 2004, Messier et al., 1997) and younger participants (Smith and Foster, 2008). Should this be the case, increased circulatory glucose and the glucoregulatory response to it (and potentially the response to the demand variable), may be targeting the hippocampus and frontal regions. Activity in these regions has previously been shown to correspond to encoding processes (Hsieh et al., 2009, Paz-Caballero et al., 2004, Wylie et al., 2008). Although it was noted that retrieval processes, including retrieval inhibition may be mediating the findings.

Examination of the potential glucose facilitation and glucoregulatory effects on retrieval inhibition processes was conducted in chapters 5 (RIF) and 6 (MBE). Glucose administration did not facilitate performance on either of these paradigms. This finding is not uncommon, with several studies reporting no glucose facilitation of memory indices (Hoyland et al., 2008, Riby, 2004). Examination of glucoregulatory control did however, produce some interesting findings. During the RIF paradigm poorer glucoregulators displayed less effective inhibition of competing semantically related stimuli. The introduction of a high effort task during encoding increased the inhibition observed in both better and poorer glucoregulators, although glucose administration did not mediate this effect.

The influence of glucose and glucoregulation on retrieval processes was further examined in chapter 6 using the MBE paradigm, whereby only orthographical similarities and not semantic / categorical links were required. Here opposing findings were observed to chapter 5, with poorer glucoregulators displaying increased inhibition but decreased executive control in order to overcome intrusive retrievals.

A considerable amount of research to date has focused on the importance of the hippocampus or demand characteristics as being preferentially targeted by glucose facilitation (e.g. Sünram-Lea et al., 2008). The novel paradigms employed within this thesis, whilst acknowledging the importance of the areas already at the heart of the glucose literature to date has widened the scope. Several of the paradigms have targeted the frontal and prefrontal regions, and found varying levels of facilitation by glucose and glucoregulatory effects on tasks known to target these areas. Such findings add further support to recent fMRI (Stone et al., 2005) and EEG (Riby et al., 2008) findings that have indicated the susceptibility of the medial-temporal and pre-frontal cortex to glucose administration. Studies which have been specifically designed to investigate the hippocampal vs. demand approaches (e.g. Smith et al., 2009b, Sünram-Lea et al., 2008) have been shown to involve these areas through ERPs. The frontal region is believed to be a key area with regards to executive control functions. The effects observed on different phases of memory within this thesis, suggest that while glucose administration has limited effects on executive control, it does appear to be differentially targeted by glucoregulatory responses. The differences in memory between better and poorer glucoregulators observed in this thesis, allows for some interesting inferences to be drawn. Firstly, memory deficits that are observed in older participants (see section 1.3.3.2.3), have previously been attributed to the associated decline in glucoregulatory control (Messier and Gagnon, 1996). However, a considerable confounding factor when investigating this population is the concurrent increase in cerebrovascular damage that also accumulates with ageing and with poor glucoregulation (Lamport et al., 2009). As this thesis concentrated on healthy young adults, who should not suffer from accumulated cerebrovascular damage, the memory impairments observed in this population may be more directly attributed to poorer glucoregulatory control in the absence of the confounding damage. Further exploration of memory in a wider context using a greater range of paradigms as per this thesis, whilst employing imaging techniques, will allow greater insight into this hotly contested area.

7.3 Blood Glucose Effects

Where circulatory blood glucose was measured (chapters 3-6), the 25 g glucose load was found to significantly raise circulatory glucose during both the high effort and low effort conditions. This finding is consistent within the literature which has administered a 25 g glucose load to young adults (see section 1.3.1.2). The increase demonstrates that treatment was successful in raising circulatory glucose levels and subsequently the availability of glucose to the brain for oxidative metabolism. In addition, the raised glucose

levels will have also evoked other glucoregulatory (see section 1.2.4) and digestive endocrine responses to the calorific treatment (see section 1.2). This finding whilst assuring that the glucose manipulation was successful, is as expected and not particularly interesting in itself. However, when glucose levels are examined in the context of the demand level of the tasks performed and the participant's levels of glucoregulatory control, some interesting results emerged.

The Remember-Know paradigm in chapter 3 revealed some intriguing findings with regard to blood glucose levels, with better glucoregulators showing higher circulatory glucose levels at pre-test prior to the high demand condition. This finding indicated that some anticipatory mechanisms may be acting in better glucoregulators that are failing / impaired in poorer glucoregulators. As median splits were performed to determine levels of glucoregulation, it is conceivable that this is a spurious finding resulting from the split, although this seems somewhat unlikely given the blood glucose levels from the glucose with low effort visit were used for this analysis. Whilst the treatment effects observed on the memory outcomes within this chapter are limited, the differences in glucoregulatory responses to the imminent onset of a demanding task here indicated that the adrenergic mechanism may be particularly influential in any potential glucose facilitation effect. While this paradigm has been investigated previously in conjunction with a glucose load, one study did not employ a high effort demand manipulation (Sünram-Lea et al., 2008) and the other employed only a high effort dual task condition (Smith et al., 2009b). As such any comparison of the effort effects on blood glucose levels between these studies is not meaningful here.

This anticipatory effect from chapter 3 was not as clearly observed in chapters 4-6, where trends (not reported) did indicate weak interactions of treatments with glucoregulatory controls although these did not reach significance. The introduction of an OGTT allowed for glucoregulation to be assessed independently of cognitive testing, which may interact with glucose administration (as indicated in chapter 3). In chapters 3, 5 and 6, visual cues such as a tripod and video camera at the testing station, in conjunction with brief rehearsal of the hand movements alerted the participants to the high demand condition following the treatment consumption. In both chapters 5 (RIF) and 6 (MBE) poorer regulators at pre and post test showed lower circulatory glucose levels during the high demand than the low demand. This may suggest increased glucose utilisation both prior to and during the task completion. Prior to the RIF task better regulators' glucose levels differed only at post test after glucose, with levels remaining elevated in comparison to the low demand task. Better regulators in chapter 6 showed greater glucose levels during low than high demand following glucose at pre and post test.

In chapter 4 (directed forgetting) no anticipatory responses were evoked since participants were not aware of the high/low demand manipulation (verbal serial three subtractions or matched number verbalisation), until immediately prior to test completion (after the pre-test blood sample was taken). The directed forgetting paradigm utilised a between subject design due to methodological constraints (deception was required prior to the recalling of items designated as to be forgotten). This unfortunately limits the scope of the glucoregulatory response data since individual variability may have biased the data. Although the overall test glucose levels in chapter 4 displayed the response curves typical of studies administering glucose, once the responses were split into better and poorer glucoregulators the response patterns were far from clear. Participants classified as better glucoregulators gave typical blood glucose response patterns, however, the poorer glucoregulators gave 'normal' response curves during low effort but not during high effort. The blood glucose responses during high effort showed greater increases in circulatory responses pre-test in response to placebo rather than glucose, with similar levels observed at post-test. This may indicate that poorer regulators within chapter 4 may not have actually been representative of a population differing in glucoregulatory control.

Several methodological differences within this thesis make it difficult to draw firm conclusions as to the inconsistent patterns of blood glucose response, between better and poorer glucoregulators following glucose consumption during high and low effort. Firstly the classification of glucoregulators was conducted using either the glucose low effort test AUC (chapter 3), or the OGTT (chapters 4-6). Secondly, changes were made to the secondary task which was employed to manipulate effort (verbal serial 3 subtractions in chapter 4, hand movements in chapters 3, 5 and 6), which may have also impacted upon blood glucose by exerting varying cognitive loads and subsequent glucose utilisation. Thirdly, the demand characteristics of the actual paradigms employed were not equal across the experimental chapters. For example the word fragment completion task during the MBE paradigm (chapter 6), required more cognitive resources for a lengthier period than the category – word stem completion task during the RIF paradigm (chapter 5). Previous research has demonstrated how manipulating the demand of a task through effort and through employment of sustained demand can influence the circulating blood glucose levels in healthy young adults (Donohoe and Benton, 1999b, Fairclough and Houston, 2004, Scholey et al., 2001, Scholey et al., 2006). Several of these studies utilised serial subtractions to induce this sustained mental effort (Kennedy and Scholey, 2000, Scholey et al., 2001), see section 1.3.5. Similar tasks were used (2 mins serial 3 subtractions, 2 mins serial 7 subtractions and 5 min RVIP) in chapters 5 and 6, which again may have influenced circulatory glucose levels.

7.4 The Impact of Glucoregulatory Control

A common theme throughout the results reported within this thesis, was the limited treatment effects that were observed on the task outcomes. However, glucoregulatory effects and interactions did present throughout, often elucidating counterintuitive findings. The assessment of glucoregulatory control was carried out in Chapter 3 (based on the area under the curve during a glucose test visit) and in Chapters 4 – 6 (using an OGTT). The influence of glucoregulatory control and its interaction with glucose administration on cognition has provided contradictory findings to date, although decrements in verbal memory seem to be the most robustly reported (Lamport et al., 2009). See section 1.3.4 for further discussion of the literature. This section will summarise the effects of glucoregulatory control throughout this thesis, which include some of the more fascinating results and potentially influential findings.

The Remember-Know paradigm employed in chapter 3 revealed that following low effort, better and poorer glucoregulators responded differently to the treatments administered when completing the recognition task. Speeded recognition responses were made by better glucoregulators having consumed the glucose load, whereas poorer regulators were speeded by the placebo treatment. This finding supports previous research in adolescents (believed to have good glucoregulatory control), which also reported glucose speeding response times Smith et al. (Smith et al., 2009b). The specific implications of these findings are not clear, but do indicate that an individual's glucoregulatory control can mediate subsequent treatment effects, with better but not poorer regulators benefitting from a glucose load.

Chapter 4 (directed forgetting) explored some particularly intriguing and counter intuitive findings. Here, better glucoregulators gave more recall errors during an immediate recall task having completed the high effort manipulation and also following glucose consumption (though no three way interaction was found). Initially this would appear to be an impairment displayed by better glucoregulators. However, upon further consideration of the data this is not necessarily the case and may indeed represent an adaptive advantage. It was postulated in chapter 4 that this finding may indicate that better regulators are attempting to retrieve items that were designated as to be forgotten. Such retrieval may be unsuccessful due to improved encoding efficiency and cessation of processing of the TBF items. Subsequently, the increase in error responses in better glucoregulators may reflect increased encoding efficiency and additionally increased tenacity in attempting to retrieve partially encoded items. This interpretation is speculative at this point, but does have the potential to aid in the identification of the specific phase (or

phases) of memory that are being targeting in the memory impairments observed in poorer glucoregulators.

While the directed forgetting paradigm in chapter 4 indicated better regulators may benefit from increased encoding efficiency and subsequent attempts to retrieve partially encoded information, chapter 5 evaluated retrieval inhibition processes using the Retrieval Induced Forgetting (RIF) paradigm. Chapter 5 presented evidence that better regulators exhibited greater RIF than poorer glucoregulators. This finding suggests that inhibition/suppression of competing information is more effective in better glucoregulators, therefore allowing greater levels adaptive forgetting of the intrusive (semantically related) information. This advantage in effective inhibition in better regulators over poorer, mirrors the findings of preserved activation and decreased inhibition in ageing populations and diseases such as DAT and Schizophrenia. These populations also co-present with an increased incidence of impaired glucoregulation (see section 1.3). Hence, decrements in inhibitory control may be being specifically targeted (or targeted in conjunction with other memory phases such as encoding), resulting in (or being partially responsible for) the overall declarative memory decrements that are observed in poorer glucoregulators.

In contrast to the findings from chapter 5, inhibition was greater in poorer glucoregulators than better when the Memory Blocking Effect (MBE) paradigm was utilised in chapter 6. Rather than contradicting the findings in chapter 5, this further supports the suggestion that adaptive inhibitory processes are being targeted / impaired in poorer glucoregulators. The most convincing evidence of glucoregulatory impact on memory blocking was seen for the number of intrusion responses made. Poorer regulators were more susceptible to intrusions than better regulators, suggesting that they may exhibit impaired inhibition of (inappropriately) retrieved items.

The glucoregulatory effects on the novel memory tasks employed within this thesis do seem to indicate that specific phases of memory are differentially impaired in individuals with poorer glucoregulatory control. Specifically, better glucoregulators seem to exhibit more adaptive inhibition of obstructive/interfering stimuli. Better glucoregulators also seemingly demonstrate greater encoding efficiency and ability to direct cognitive resources effectively to achieve ‘better’ performance on the declarative memory tasks employed here. It should be noted here that the population sampled within this thesis were self reportedly healthy young adults, with no known cognitive or glucoregulatory impairments. Whilst it would be premature to conclude that these findings are robust and can be generalised to abnormal populations, they do provide some interesting insight into

the potential memory processes/phases that may be responsible for the reported memory impairments within populations presenting with poor glucoregulatory control.

7.5 Task Effort / Demand

The inclusion of a high effort / dual task, was initially included as a variable of the research within this thesis, as glucose has been shown to reliably enhance cognitive functioning in healthy young adults during conditions of divided attention at encoding (Foster et al., 1998, Sünram-Lea et al., 2002a, Sünram-Lea et al., 2001, Sünram-Lea et al., 2002b, Sünram-Lea et al., 2004), see section 1.3.5.for further details. The effort manipulations employed throughout this thesis (also during encoding) were found to be highly effective in inducing memory deficits (chapters 3 and 4) and interacting with glucoregulation on retrieval and inhibition process (chapters 5 and 6).

One of the difficulties within the data of this thesis is that the effort manipulation was always induced during the encoding phase of stimuli presentation. The placement of the dual task in this thesis is in line with that of the glucose literature methodology (Foster et al., 1998, Sünram-Lea et al., 2002a, Sünram-Lea et al., 2001, Sünram-Lea et al., 2002b, Sünram-Lea et al., 2004). However, as a consequence of this, paradigms which were not directly concerned with the encoding phase per se e.g. RIF and MBE, may have displayed very different effects had the positioning of this the dual demand been employed at the relevant stage of the memory process of concern. Although such a manipulation would have involved further novel techniques to be super imposed on already novel paradigms within the glucose and cognitive literature.

The positioning of the high effort task did however, lead to some very interesting findings, not only on RIF (chapter 5 and section 7.2.4) and MBE (chapter 6 and section 7.2.5), but also on performance during the filled retention period tasks. Here a ‘carry over’ effect was observed, with high effort facilitating performance advantages during the subsequent demanding serial sevens subtraction task, although this effect was more evident in chapter 5, when a repeated cuing phase was completed prior to the retention period tasks. In chapters 5 and 6, a filled retention period of 10 minutes was comprised of 2 min serial 3 subtractions, 2 min serial 7 subtractions and 5 min RVIP task. Earlier chapters (3 and 4) had employed long hand multiplications, but the decision to move away from this was driven by participants not seeming to fully engage with the task. By changing the tasks, participants should have remained engaged throughout the 10 min period and this could be accurately assessed.

This raises the possibility that the increased susceptibility to memory facilitation, as reported in the literature (Foster et al., 1998, Sünram-Lea et al., 2002a, Sünram-Lea et al., 2001), may not be due to the increased difficulty induced via divided attentional resources during encoding. It may be that it is this 'carry over' effect during the consolidation period that is eliciting the effect. However, dividing attention during encoding undoubtedly limits encoding resources, decreasing capacity for elaborate encoding and subsequently influences later performance and likely, the retrieval and inhibition processes assessed within this thesis.

One way to test this would be to employ demanding tasks at various stages of the test session to investigate any subsequent performance effects. For example, by subjecting participants to a highly demanding task immediately prior to word display, there may be an increased capacity for encoding resources elicited by the 'carry over' effect. This may be measurable using the DF paradigm, by moving the highly demanding task (verbal serial 3s was used here during the encoding phase), to be administered pre encoding. Although the task difficulty would have to be increased substantially since the dual nature of the task is key to the increased demand here. To some extent, the high demand aspect has already been employed immediately prior to consolidation (RIF) and prior to retrieval with the employment of the filled retention task. However, by varying the difficulty / demand of the tasks, a greater insight into the strength of the effect may be gained.

Whilst glucose is raised following consumption it may be that it is the concurrent stress that elicits an adrenergic or glucocorticoid response that elicits the subsequent facilitation of declarative memory. This issue is considered further in the next section.

7.6 Stress

The finding that glucose facilitation is most robustly observed under conditions of divided attention during encoding (Foster et al., 1998, Sünram-Lea et al., 2002a, Sünram-Lea et al., 2001) may indicate that performance is being influenced by hormones such as adrenaline and cortisol (Gibson, 2007). Both adrenaline and cortisol are released in response to stress through the activation of the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis respectively. They have both been shown to influence performance and also mediate glucoregulation (for further explanation of the adrenergic mechanism and the influence of glucoregulation see section 1.4). It has been postulated that the HPA axis may be one potential mechanism by which glucoregulatory

efficiency mediates glucose facilitation (Smith et al., 2009a). The administration of cortisol shares several characteristics with the administration of glucose, providing convincing evidence that evoked cortisol is an influential factor in mediating the glucose effect. Firstly, there is evidence that cortisol administration displays an inverted-U dose response effect on memory improvements (Abercrombie et al., 2003). Secondly, a glucose load prior to a stressful task has been shown to elicit a greater cortisol response (Kirschbaum et al., 1997), with cortisol facilitating recall of emotional stimuli but impairing neutral declarative memory (Abercrombie et al., 2003, Abercrombie et al., 2006, Abercrombie et al., 2004, Buchanan and Lovallo, 2001, Kirschbaum et al., 1996). This is somewhat reminiscent of the glucose facilitation of emotional material and impairments following reduced circulating glucose (Brandt et al., 2010, Brandt et al., 2006, Scholey et al., 2003, Scholey et al., 2006). Further as observed with glucoregulation, cortisol follows the circadian rhythm, with greater release in the morning and declining over the course of the day.

High effort manipulations were incorporated into chapters 3-6, as healthy young adults have previously been shown to be more susceptible to glucose facilitation during highly demanding tasks loading (Foster et al., 1998, Sünram-Lea et al., 2002a, Sünram-Lea et al., 2001, Sünram-Lea et al., 2002b, Sünram-Lea et al., 2004) (also see section 1.3.5). As described above, this manipulation is likely to have evoked a stress response in participants completing the high effort tasks, inducing a corresponding release of cortisol and/or adrenaline. In chapters 4-6 subjective stress/state anxiety was measured through a 'stressed' VAS and also via the SF STAI. Whilst these measures can not directly quantify the HPA axis response during a testing session, inferences may be drawn in conjunction with the circulatory blood glucose measures (the effects of which are given in section 7.3).

The research within this thesis found very little evidence that glucose, glucoregulation or effort acted independently or in combination to exert a measurable impact on an individual's self reported stress levels and anxiety state. In chapter 4, self reported stress was shown to increase over the test session; however, this increase was not mediated by treatment, effort or glucoregulation. In chapter 5, better glucoregulators reported increased anxiety (SF STAI scores) at post test compared to poorer glucoregulators, but no effort or treatment effects were apparent. In chapter 6, poorer glucoregulators reported increased SF STAI scores at post test following glucose, however, no effort effects were observed on self reported stress levels.

These findings suggest that while the dual task / high effort manipulation did mediate aspects of memory, the manipulation did not induce measurable self reported stress in participants. This lack of effort effects may be due to the insensitivity of the measures used, and / or the placement of them. Stress measures were taken pre and post test, which was approximately 20 minutes after the high effort manipulation had been completed, although this varied slightly with the paradigm employed. Subsequently it seems likely that any increased subjective feelings of stress had not been evoked prior to the task completion, and may have also subsided before the post test measure had been completed (had any such increase been induced). A non-subjective physiological measure of HPA axis activity (e.g. sampling salivary cortisol) may have revealed more evidence here. However, the limited effects observed on circulatory blood glucose levels and on memory indices do indicate that HPA axis activation may have exerted an influential mediating effect on outcomes within this thesis.

7.7 Mood and Satiety

7.7.1 Mood

To date the influence of glucose and glucoregulation on mood are unclear, with contradictory findings reported. Of the studies which have included measures of mood, these outcomes have generally been secondary outcomes in research primarily focusing on other aspects of cognition, as has been the case throughout this thesis.

A recent dose-ranging study reported no mood effects in healthy young adults regardless of the dose consumed (Sünram-Lea et al., 2010). Scholey et al. (2009b) found both placebo and glucose (the same treatments administered in chapters 3-6) increased 'alertness' over the testing period, which is in line with studies administering water to increase hydration status (Neave et al., 2001, Rogers et al., 2001). However, a review indicates that mood changes are variable dependent upon the type of carbohydrate consumed and also the timing of mood measures (Benton, 2002). Benton also reported that there is a tendency for those with lower blood glucose when performing cognitively demanding tasks, to report poorer mood. Additionally, rapid decline in blood glucose levels tended to be associated with irritability (Benton, 2002).

In chapter 2, children were asked to report how awake they felt using computerised VAS. This was found to increase over the course of the testing visit irrespective of the treatment

received. This finding lends some support to Scholey et al. (2009b) who reported increased alertness although over a much shorter test period and in an older population. In chapter 5 better glucoregulators were found to show decreasing alertness over the testing session, with calmness increasing over the visit following placebo but not glucose. Very little consistency was observed on mood measures across the chapters. In chapter 6, levels of contentment declined over the session in poorer glucoregulators. Whilst no discernable effect patterns of treatment or glucoregulation are apparent throughout this thesis, mood outcomes do appear to be sensitive to these manipulations. The inconsistent findings reported here, may be in part down to the tasks themselves and the unique demand characteristics. For example, the fragment completion task during the MBE paradigm in chapter 6 was (anecdotally) reported to be very challenging and frustrating, whereas the repeated cuing phase during the RIF paradigm was not found to be particularly challenging.

7.7.2 Satiety

Satiety measures of thirst and hunger were not initially of concern when the research for this thesis commenced. However, over the course of interpreting the results and the potential underlying factors accounting for them, the importance of physiological status other than that of glucose (directly) and glucoregulatory control became apparent. The role of hydration and appetite and their potential influence on the findings within this thesis are discussed in this section.

7.7.2.1 Hydration Status and Cognition

The literature investigating hydration status on cognition is at present quite limited. The majority of studies which have investigated this area have induced dehydration through physical exertion or heat stress (Grandjean and Grandjean, 2007, Lieberman, 2007, Maughan et al., 2007b). While this does have environmental relevance for those individuals who must maintain function following exertion (e.g. military personnel), these studies do not reflect the status or influence of hydration in individuals presenting in their normal everyday state. Furthermore, it is difficult to disentangle the effects of dehydration on cognition from that of the stressor used to induced the dehydration (Grandjean and Grandjean, 2007).

The role of hydration status when considering glucoregulation may be of greater importance than has been considered within the glucose literature to date. Several of the studies which have investigated populations with poorer glucoregulation have used older adults (see sections 1.3.4) who in conjunction with decreased glucoregulation, exhibit a decrease in thirst mechanisms with an associated increase in susceptibility to dehydration (Buyckx, 2007). In diabetics, dehydration has also been shown to be associated with higher blood pressure during the day and a smaller reduction in overnight blood pressure (Buyckx, 2007). Continuous hypertension may further confound the vascular damage which is believed to contribute to the cognitive impairments reported in diabetes and the metabolic syndrome (Ryan, 2006) (see section 1.3.3.1.1 for further consideration diabetes and the metabolic syndrome). This evidence highlights the (potential) susceptibility of poorer glucoregulators to dehydration and consequent impaired cognitive functioning.

Research investigating young adults has shown that even mild dehydration can lead to significant impairment in cognitive function. It has been suggested that dehydration of 2 to 3% body weight loss leads to decrements in cognitive functioning (Lieberman, 2007), although dose ranging response studies have reported significant decrements (reduction in correct serial additions) at only 1% body weight loss dehydration (Gopinathan et al., 1988, Lieberman, 2007). The mechanisms underlying thirst and cognition are not well understood, but include complex interactions between biochemical, physiological, neural and learnt processes (for reviews see; Bourque, 2008, McKiernan et al., 2008). The major physiological factors which signal dehydration and subsequent 'thirst' relate to osmolarity (increases in cerebrospinal fluid and blood) and volume (of the extracellular fluid [ECF]). These include the balance of electrolytes, which have the potential to alter brain neurotransmission (Lieberman, 2007), along with reduced cerebral blood flow (Maughan et al., 2007a) and hence cognition.

The specific aspects of cognition that are targeted by even mild dehydration have not yet been entirely determined, with some contradictions in the limited evidence to date. Using fluid deprivation as a route to dehydration (fluids withheld for 28 hrs, with water content of the food consumed less than 75%), Szinnai et al. (2005) elicited 2.6% dehydration. Here no cognitive deficits were observed on the tasks completed (Stroop, paced auditory serial addition, choice RT and a manual tracking task). Dehydration was however, found to reduce alertness and concentration, with increased levels of tiredness and perceived effort. Similar self reported measures effects were reported by Shirreffs et al. (2004), following 2.7% dehydration.

The relationship between fluid consumption, hydration and cognition is not straightforward. Rogers et al. (2001) administered water (120 ml or 330 ml) to participants presenting in their natural hydration and appetitive state. Rogers et al. reported immediate (but not sustained) increases in reported alertness and 'revitalisation' following the drink of water, however, performance on the RVIP task was mediated by initial thirst. High thirst led to a dose-related improvement in performance on the RVIP task, but in contrast low initial thirst showed a dose-related impairment in performance. A similar study completed a partial replication of Rogers et al.'s. (2001) study, with additional controls (fasting from midnight prior to testing) and testing 150 ml of water consumption against a no treatment control (Neave et al., 2001). Neave et al. also employed a greater range of cognitive tasks (CDR test battery; RVIP, word recall, simple RT, digit vigilance, choice RT, spatial working memory and numerical working memory). Here, in contrast to Roger et al.'s (2001) study, water was not found to facilitate or impair any aspect of measured cognitive function, although water did increase subjective 'alertness'. However, differences in the initial thirst state of participants (fasted as opposed to natural) along with task duration (3 min RVIP in Neave et al. as opposed to 6 min in Rogers et al.) may account for the differences in findings.

In adults a double dissociation on memory facilitation (word recall) has been reported between initial thirst and a glucose drink (Scholey et al., 2009b). Scholey et al. (2009b) administered the same glucose and placebo drinks as used in chapters 3, 4, 5 and 6 of this thesis (25 g glucose / saccharine in 200 ml). This glucose drink is hypertonic and is approximately twice the osmolarity of plasma / ECF (~0.3 Molar), being 0.69 Molar (Scholey et al., 2009b). Hypertonic drinks are also associated with gastrointestinal discomfort and nausea (Phillips et al., 1996). A further consideration is that different beverages, in spite of being the same volume actually have varying functional water volume. For example 100 g of water results in 100 ml of functional water volume, whereas 100 g of 10% glucose solution only has a functional water volume of 60 ml (Manz, 2007). In addition, drinks with a high carbohydrate content are much less thirst quenching than equivalent volumes of water (Manz, 2007). Research which compared the effects of water to saccharine has demonstrated that performance was not influenced differently by the two drinks, suggesting that saccharine is an appropriate placebo emulating similar effects to water in isolation (Messier et al., 1998). Scholey et al. (2009b) reported amongst those with low initial thirst, more word items were recalled following glucose than placebo, with the high thirst group showing the opposite; more word items following placebo than glucose. The findings from Scholey et al. (2009b) make sense when thirst is considered in conjunction with the volume of the drinks. Participants who reported to be less thirsty were able to exhibit glucose facilitation of memory, whilst those

who were thirstier gleaned greater benefit from the increased functional water volume of the placebo. These findings demonstrate a bias in performance benefit to treatments which a) return bodily homeostasis resulting in cognitive facilitation / decreasing decrements to 'normal' levels and b) allow for further cognitive enhancements above 'normal' levels by additional resources once homeostasis is achieved.

Children are at greater risk from dehydration than adults due to their higher surface-to-mass ratio and also through the dependence upon others to provide sustenance. Dehydration in infants is associated with confusion, irritability, and lethargy; in children, it may produce decrements in cognitive performance (D'Anci et al., 2006). In a study encouraging ad libitum water consumption in 7-9 yr olds 20 minutes prior to cognitive task completion (letter cancellation and spot the difference memory task), those consuming water were found to show better visual attention and memory (Edmonds and Burford, 2009). A 300 ml drink of water in the afternoon was found to facilitate better memory in the form of increased recall, but not sustained attention in 8 yr olds (Benton and Burgess, 2009).

A glucose drink administered to children (6-7 yr olds) was observed to decrease frustration and increase sustained attention (Benton et al., 1987), which would be consistent with reversing any dehydration effects as described by D'Anci et al. (2006) and is in line with the attention findings of Edmonds and Burford (2009). Benton et al. (1987) compared the glucose drink to a saccharine placebo drink and as such the potential hydration effect cannot be fully dissociated, since both treatments were of equal volume and both may have influenced cognitive performance. However, the isotonic content of the drinks will have varied, influencing the speed of absorption in addition to the varying functional water volume.

In chapter 2, 150 ml drinks were administered with 0 g (saccharine placebo), 20 g or 40 g of glucose in water. While no effect were observed on memory outcomes, the impairments observed following 20 g glucose on the arrow flankers task (see section 2.4.2.3), compared to placebo and 40 g glucose may well have been a consequence of the hypertonic nature of the drink. This may have disrupted the balance of electrolytes (which has the potential to alter brain neurotransmission) (Lieberman, 2007), raised the osmolarity of circulating blood and cerebrospinal fluid and / or negatively impacted the volume of ECF. Furthermore, hypertonic concentrations of glucose may result in gastrointestinal discomfort and nausea (Phillips et al., 1996), which may influence performance. However, if these factors were to be the underlying cause of the impairment observed in chapter 2, it would seem logical that a 40 g glucose load would further disrupt

these potential mechanisms leading to greater impairments. This was not observed and it is postulated that the facilitating effect of glucose on cognition, when administered in sufficiently high doses, can overcome the impairments induced by the hypertonic drink.

The findings of Scholey et al. (2009b) have important implications on the research investigating the effect of glucose on cognition, including the research within this thesis. Chapters 4, 5 and 6 gathered subjective measured of thirst at baseline, pre-test and post-test. The studies were not designed to investigate the role of initial hydration (or satiety) status on the primary task outcomes and they did not reveal any definitive effect patterns. The dosages utilised within the literature vary, but 25 g and 50 g glucose loads are the most often associated with cognitive facilitation (see sections 1.3.1.2 and 1.3.3). However, the difference in functional water volume and osmolarity between the doses, may elicit very different mechanisms not only of the potential glucose mechanisms described in section 1.4, but also the hydration mechanisms described above. The hydration mechanisms may act to influence cognition independently of the actual glucose effect. This problem is further confounded as the volume of the glucose drinks administered is not consistent across the literature and different research groups. The volume of 200 ml was utilised in chapters 3, 4, 5 and 6 although within the literature volumes have ranged from as low as 150 ml (Ford et al., 2002a), through to 300 ml (e.g. Smith et al., 2009b). The cumulative effects of these seemingly small differences between the methodologies employed within the glucose literature, may account for (some of) the variability and inconsistency of effects of glucose and glucoregulation on cognition, memory in particular.

Consequently whilst the potential importance of thirst and hydration status on cognition is acknowledged, it cannot be meaningfully disentangled from the data within this thesis although hints that thirst may be influential in mediating the effects of glucose on cognitive performance.

7.7.2.2 Appetite and Cognition

The administration of glucose in the form of a drink makes it easy to overlook the calorie content of the treatment being administered. Consumption of a calorific drink evokes not only hydration regulation mechanisms, but also appetitive responses.

Ghrelin (a hormone released primarily by the stomach) stimulates appetite (Hurlbert, 2007). It has been shown to affect several physiological processes including appetite

regulation, metabolism and, more recently cognition (Carlini et al., 2008, Carlini et al., 2002, Diano et al., 2006). Although much of this research has been conducted in rats, it draws attention to the fact that when administering a glucose load (calorific) or placebo (non-nutritive), the endocrine responses are not limited to the well known glucoregulation hormones (insulin, glucagon etc), but actually influence a far greater spectrum such as ghrelin and leptin. Leptin (produced from adipose tissue) is regarded as the counterpart to ghrelin and plays an important role in signalling the status of long term (fat) energy stores and long term inhibition of appetite (Hurlbert, 2007). Research in rats has also revealed that leptin can act as a potential cognitive enhancer, acting on the hippocampus (as does ghrelin) to enhance memory (Harvey et al., 2005).

The potential interactions between administration of a glucose load, glucoregulatory responses and appetitive endocrine responses have been to date, largely ignored within the glucose cognitive literature. Only through physiological measurements of such responses, could the relationships be disentangled which is often beyond the scope of the research being conducted. However, with the lack of robust glucose effects on cognition to date, perhaps incorporation of such measures will allow a more precise examination of how glucose is influencing memory. The only study (to the authors knowledge) that has attempted to assess the role of 'hunger' on cognitive performance is Scholey et al. (2009b) as mentioned in the previous section. Whilst thirst was found to interact with the glucose / placebo administered to mediate subsequent cognitive performance, the results were less clear for hunger. Scholey et al. (2009b) reported a trend for slower word recognition in those with high initial hunger.

Although the evidence is far from definitive, better glucoregulators may be more accurate at detecting the calorific content of the drinks consumed, which is then reflected in their subsequent 'hunger' ratings. This was certainly apparent in children (chapter 2), who's self reported 'fullness' levels accurately reflected the glucose load consumed (greater hunger following 20 g of glucose than 40 g). Perhaps this is not a surprising finding, since better glucoregulation implies that all aspects contributing to glucose regulation are working synergistically to maintain homeostasis. However, this tentative finding may also indicate that any decrements / enhancements in cognition following a glucose load in poorer regulators, may be in part attributable to appetitive hormones such leptin and ghrelin, the actions of which can mediate cognition (Carlini et al., 2008, Diano et al., 2006, Harvey et al., 2005).

When evaluating the self reported hunger levels in chapters 4, 5 and 6, there did not appear to be any clear response patterns (to the 'Hunger' VAS) that indicated an accurate

sensing of calories consumed in the treatment. Nevertheless, differences in appetite hormones to the active vs. placebo treatment may have acted to mediate cognitive performance. A potential limitation however, was that all participants had completed a fasting period prior to testing, as such the normal breakfast eating habit may have influenced individuals perceived hunger levels.

The studies within this thesis were not designed to assess the interaction between initial thirst and hunger with glucose and glucoregulation on cognition. However, the potential influence of these factors on the findings should not be ignored. These factors may have mediated task performance throughout this thesis and also of the glucose literature published to date. Subsequently, several recommendations and potential avenues for future research can be suggested. The incorporation of a no treatment condition into the study designs would better enable any hydration effects of the treatments to be investigated through comparisons of the placebo with no treatment. Incorporating measurements of various physiological responses throughout testing would enable investigation of the effects of hormones such as leptin and ghrelin on performance.

7.8 Potential Limitations

The experimental chapters of this thesis are very much independent in terms of the methodology and task paradigms employed. Several potential methodological limitations have been covered within the discussion of each of the chapters in turn (section 7.2.1 to 7.2.5). This section takes a broader overview of the limitations of the scope of this thesis.

The previously published literature pertaining to the glucose and glucoregulatory effects on verbal declarative memory is currently limited to overall memory tasks (word display with an immediate / delayed recall and / or recognition phase). Upon initiating the research for this thesis, there was no structure in place within the glucose literature to investigate the distinct memory phases independently of each other. Consequently it was necessary to employ novel techniques and paradigms from the cognitive research area, in order to investigate whether the reported glucose facilitation and glucoregulation indices were specifically targeting specific phases of memory. This has enabled some interesting findings to be investigated, however, as the paradigms are unique in this area of research, it is difficult to draw firm assertions as to the absolute meaning of the findings. The lack of comparative studies also means that the robustness of the findings within this thesis cannot at present be qualified.

The lack of glucose effects on memory observed within this thesis was somewhat surprising in light of the accepted robustness of the effect. Throughout this thesis many trends were evident in almost all of the paradigm outcomes. However, in order to maintain the integrity of the work, the decision was made to concentrate on significant findings ($p<0.05$) (although there were some trends reported within the thesis, as these were deemed to be informative in the context of the remainder of the results reported). This conservative approach may have camouflaged potentially informative effects which failed to reach significance due to the underpowered nature of the sample sizes employed. This decision may also narrow the scope of future research generated from the findings within this thesis. Subsequently the power of the study designs is considered here.

The lack of treatment effects may be a direct consequence of the studies within this thesis being underpowered to detect small and medium effects. Priori power analyses were not conducted for the studies presented within this thesis. Sample sizes were selected to reflect those commonly utilised within the glucose literature, which have previously been shown to detect effects of glucose on memory. However, in hindsight this was not the most desirable approach to take. For example, a priori power analysis (conducted using G*Power 3) for a mixed design (as employed in chapters 3, 5 and 6), indicated that a total sample of 82 participants would be required to detect a medium effect size ($r=0.25$) with a power of 0.8 (0.8 is the convention for a desirable level of power (Rosenthal et al., 2000)). Post hoc computations of achieved power for a sample of 20 in such a design was only 0.27 for outcomes with a medium effect size ($r=0.25$), which falls far short of the desired 0.8 power level. For a sample size of 20 (as used in chapters 3, 5 and 6), only large effect sizes (specifically $r=0.525$) achieve the desired power of 0.8. In summary, this indicates that small and medium effects are unlikely to have been detected throughout this thesis, with type II errors likely to have been made. These smaller (potentially undetected) effects are likely to be interesting and may well account for the lack of treatment effects observed, which are conceivably small effects in the healthy population sampled.

Perhaps the largest limitation of the methodology employed throughout this thesis was the use of median splits to assign participants as better or poorer glucoregulators. This approach incorporates several potentially detrimental factors, particularly within chapter 4. Firstly, the use of median splits allowed analysis of performance in terms of better vs. poorer glucoregulators within each chapter (3-6). However, as each chapter tested different participants, the range of glucoregulatory control exhibited by participants was also variable across the chapters. A consequence of this is that a ‘better’ glucoregulator in one chapter may have been grouped as a ‘poorer’ glucoregulator had they been

assessed as part of a different study. This is an issue across the literature and one that is difficult to overcome. Chapter 4 employed a between participants design (necessarily so due to the deception within the paradigm), with condition randomly allocated on enrolment into the study and the glucoregulation median split conducted after all testing had been completed. This resulted in uneven groups and reduced statistical power. An alternative approach would have been to administer all oral glucose tolerance test and grouping to better or poorer glucoregulation groups before condition allocation. However, this would have been extremely time consuming (since participants were tested individually) and would have elicited a longer delay between assessment for glucoregulation and the test visit. Glucoregulation is very variable with many mediating factors (even the meal prior to the test). A recent systematic review reported that the reproducibility of an OGTT from 2 tests less than 8 weeks apart ranged from only 33% to 48% (Balion et al., 2007). As such it was not deemed appropriate to incorporate a long delay between OGTT and testing.

Utilising a median split for glucoregulation halved the number of participants per group, further confounding the already small group sizes. Add to this the uneven groups (particularly in chapter 4) and the loss of power is considerable. In order to circumvent this issue, utilising more homogenous groups when considering glucoregulation would have decreased standard deviation and increased the relative effect sizes. This could have been achieved by removing the "middle" portion of glucoregulators from the analysis, to consider only the extremes of 'better' and 'poorer' glucoregulators studied. This however, would have again further reduced the sample sizes.

Furthermore, there are a variety of indices on which participant's glucoregulation may be grouped (e.g. OGTT or test total area under the curve, baseline adjusted OGTT or test area under the curve, peak evoked glucose levels etc). Each of these have their relative merits and are potentially indicative of different aspects of glucoregulation. Chapters 4-6 of this thesis utilised the 60 minute OGTT glucose level minus baseline glucose levels. This index was selected for two reasons; it is has been shown to correlate with cognitive performance previously (Messier et al., 2003) and also, as testing occurred during this time period it was deemed appropriate to use an index of glucoregulation that represented the glucoregulatory factors that would be influential over the testing period.

Finally, treatment order effects may have influenced the findings reported within this thesis. In chapter 2, where multiple participants completed the same treatment orders, order effects were considered. No interpretable effects were found, although previous research has indicated that order effects can influence the results (Benton and Stevens, 2008, Smith and Foster, 2008). In chapter 3, a between participants design was used

negating any influence of order effects. Whilst chapters 4 – 6 employed repeated measures designs, no two participants completed the same order of conditions, as such consideration of order effects was not deemed appropriate. Nonetheless, carry over effects from prior visits/treatments may have exerted an influence on subsequent task performance.

7.9 Future Research

While the limitations covered in section 7.8 highlight several issues within this thesis that should be addressed in future research, there is also considerable scope for future research resulting from the results of the series of studies presented here.

The selection of novel paradigms utilised within this thesis, represent only a small proportion of those available from the cognitive sciences literature. Replication of the findings within this thesis would be an important first step in confirming the reliability of the conclusions drawn from this research within this thesis. Particularly the inclusion of physiological measures in order to accurately assess the glucoregulatory endocrine response (insulin etc), hydration status and satiety response (leptin, ghrelin etc) and activation of the HPA axis (cortisol and adrenaline), would allow a far broader understanding of the body's response to the paradigms and subsequently the potential mechanisms which may be mediating performance. However, such physiological measures are substantially more invasive for the participant and more costly to fund.

Expanding the selection of the novel paradigms utilised, will allow further insight into the intricacies of glucose and glucoregulatory effects on verbal declarative memory. Likely paradigms would include the Deese-Roediger-McDermott paradigm (which evokes false memories of semantically related items), the word list method of directed forgetting (this alternate version of that employed in chapter 4 measures retrieval inhibition rather than encoding efficiency) or the tip of the tongue (TOT) phenomenon which is closely linked to the MBE investigated in chapter 6.

Several of the paradigms employed within this thesis lend themselves well to being used in conjunction with imaging techniques, such as EEG, and fMRI (and indeed these techniques have been employed within the cognitive literature). By employing these techniques in conjunction with comparisons across treatments (and from the results reported in the cognitive literature), a better understanding of the brain areas that may be being mediated by a glucose load and /or glucoregulation may be achieved. The

Remember Know paradigm as employed in chapter 3 has already been utilised successfully in this way with EEG (Smith et al., 2009b).

An important progression of the research within this thesis would be the evaluation of the effects on a range of populations. Testing participants across a wide age range, and patient populations presenting with a range of glucoregulation disorders (e.g. metabolic syndrome, diabetes), would further this work and enable greater dissociation of the role of glucose and glucoregulation on memory.

Finally, the 'carry over' effect that was observed following the high effort dual demand task warrants further investigation. Utilising a secondary task in which the intensity / demand characteristics can be varied would allow an examination of whether the level of demand characteristics induced proportionately mediate the carry over effect. As an example, a more or less challenging dual task may lead to a greater or reduced RIF magnitude to be induced as the repeated retrieval phase is completed immediately following the dual task. A further means to examine the 'carry over' effect would be to move the highly demanding task. For example completion of a demanding task immediately prior to encoding may have a carry over effect of improving encoding, or if completed immediately prior to the DF paradigm, increased directing forgetting may be evident.

7.10 General Conclusions

The principal aim of this thesis was to begin to establish if glucose preferentially facilitated specific phases of verbal declarative memory. Whilst the glucose facilitating effect on memory has been investigated for over 25 years, there remains contradictory evidence and large voids in existent knowledge. The previous literature has generally used well established validated tasks, employing word recall and recognition. However, methodological differences between studies make direct comparisons difficult to draw and may account for the inconsistencies within the reported findings.

While the paradigms that were employed within this thesis all aimed to assess the influence of glucose and glucoregulation on declarative memory, each paradigm was selected so as to manipulate different aspects of memory encoding, consolidation and or retrieval. The novel paradigms utilised here have been well established within the cognitive literature, where they have been used to assess memory and memory changes across different populations.

Whilst the evidence within this thesis is in places tentative, some intriguing postulations have been made, opening several interesting avenues for further investigation. The conclusions devised from this thesis can be surmised as follows:

- In children, the effects of glucose on cognition remain unclear. The relationship between satiety, the tonicity of the drink administered and the influence of glucose appear to be highly interdependent and difficult to dissociate (using non-invasive methodology). However, based upon the findings presented here, glucose does not appear to facilitate memory or other aspects of cognition in this population.

- Specific recognition types (familiarity and recollection) do not appear to be preferentially targeted by glucose, indicating that any glucose facilitation may be acting via a more global demand related mechanism, rather than specifically targeting the hippocampal domain.

- Tentative evidence suggests that encoding may be targeted by glucose administration and mediated by glucoregulatory control. Better glucoregulators following glucose administration and also following the high effort manipulation, were more likely to make tenacious (but still unsuccessful) attempts to retrieve items that had not been fully encoded. This paradigm has been shown to activate both the hippocampus and frontal areas of the brain, suggesting that these areas may be being targeted by glucose in better glucoregulators.

- Glucose does not seem to influence inhibition processes, however, glucoregulatory processes do. Better glucoregulators demonstrated greater inhibition of semantically related materials (through increased RIF of non practiced items from cued categories), which aids memory efficiency. However, poorer glucoregulators demonstrated greater inhibition of orthographically similar but semantically dissimilar items from recall (through increased intrusions responses during the MBE paradigm), which is a maladaptive inhibition. Consequently even in healthy young adults poorer glucoregulation is associated with decreased adaptive and greater maladaptive inhibition processes.

- The dual task / increased effort manipulations employed within this thesis suggest that glucose is not simply increasing attentional capacity during encoding of the information where the manipulation was completed. It was postulated that both anticipation of an imminent demanding task and ‘carry over’ effects following the high demand may be mediating any memory facilitation. This may indicate that

the activation of the HPA axis and stress hormones are key features in mediating memory performance here.

APPENDICES

APPENDIX 1. PARTICIPANT CHARACTERISTICS

Appendix 1.1 Chapter 2 Participant Characteristics

PARTICIPANT NO.	DOB	AGE	SEX	ETHNICITY	BMI	GLASSES	HANDEDNESS
001	10/03/1997	10	F	CAUCASIAN	17.9	N	RIGHT
002	13/02/1997	10	M	CAUCASIAN	17	N	RIGHT
003	23/06/1997	10	F	CAUCASIAN	21	N	RIGHT
004	16/02/1997	10	F	CAUCASIAN	19.2	N	RIGHT
005	06/10/1996	10	M	CAUCASIAN	18.8	N	RIGHT
006	18/07/1997	10	M	CAUCASIAN	16.6	N	RIGHT
007	05/12/1996	10	F	CAUCASIAN	18.1	N	RIGHT
008	19/01/1997	10	M	CAUCASIAN	16.1	N	RIGHT
009	02/10/1996	10	M	CAUCASIAN	20.8	N	LEFT
010	17/11/1996	10	F	CAUCASIAN	17.1	N	RIGHT
011	04/10/1996	10	M	CAUCASIAN	20	N	RIGHT
012	06/05/1997	10	M	CAUCASIAN	21	N	RIGHT
014	03/03/1997	10	F	CAUCASIAN	18.1	N	RIGHT
015	13/05/1997	10	M	CAUCASIAN	20.9	N	RIGHT
016	05/02/1997	10	F	CAUCASIAN	14.8	N	RIGHT
017	18/11/1996	10	F	CAUCASIAN	21	N	RIGHT
018	21/04/1997	10	M	CAUCASIAN	21	N	LEFT
019	03/02/1997	10	F	CAUCASIAN	19.4	N	RIGHT
020	14/09/1996	10	M	ASIAN	20.8	N	RIGHT
021	04/10/1996	10	F	CAUCASIAN	19.4	N	RIGHT
022	01/01/1997	10	F	CAUCASIAN	16.6	N	LEFT
023	17/06/1997	10	F	CAUCASIAN	17.6	N	RIGHT
024	31/05/1997	10	F	CAUCASIAN	21.8	N	RIGHT
025	14/11/1996	10	F	CAUCASIAN	19	N	RIGHT
026	04/05/1997	10	F	CAUCASIAN	15.8	N	RIGHT
027	07/10/1996	10	F	CAUCASIAN	18.5	N	RIGHT
028	05/11/1996	10	F	CAUCASIAN	14	N	RIGHT
029	11/01/1997	10	M	CAUCASIAN	15.8	N	RIGHT
030	10/05/1997	10	F	ASIAN	18.4	Y	RIGHT
031	09/12/1996	10	M	CAUCASIAN	18.4	Y	RIGHT
032	16/10/1996	10	M	CAUCASIAN	15.8	N	LEFT
035	22/01/1997	10	F	CAUCASIAN	19.8	N	RIGHT
036	18/12/1996	10	F	IRANIAN	20.1	N	RIGHT
038	04/01/1997	10	F	CAUCASIAN	18.8	Y	RIGHT
039	08/03/1997	10	F	CAUCASIAN	15.7	N	RIGHT
040	11/10/1996	10	F	CAUCASIAN	14.7	N	LEFT

Appendix 1.2 Chapter 3 Participant Characteristics

PARTICIPANT NO.	GLUCO-REGULATION	DOB	AGE	SEX	ETHNICITY	BMI	WHR	GLASSES	HANDEDNESS
001	POORER	09/06/1979	27	M	CAUCASIAN	26.6	0.89	N	RIGHT
002	BETTER	21/02/1984	23	M	CAUCASIAN	26.8	0.97	N	RIGHT
003	POORER	10/02/1982	25	F	ORIENTAL	22.2	0.76	Y	LEFT
004	POORER	02/11/1981	25	F	CAUCASIAN	20.3	0.79	N	RIGHT
005	POORER	16/06/1984	22	M	CAUCASIAN	21.0	0.83	Y	RIGHT
006	BETTER	22/08/1974	32	M	CAUCASIAN	25.4	1.05	N	RIGHT
007	POORER	23/05/1984	22	M	CAUCASIAN	24.0	0.89	N	RIGHT
008	POORER	16/08/1984	22	F	CAUCASIAN	21.4	0.81	N	RIGHT
009	BETTER	02/11/1983	23	M	CAUCASIAN	25.5	0.88	N	RIGHT
010	POORER	25/09/1975	31	F	CAUCASIAN	22.2	0.78	N	RIGHT
011	BETTER	22/11/1972	34	M	CAUCASIAN	26.5	0.98	N	LEFT
012	BETTER	08/04/1971	36	M	CAUCASIAN	26.2	0.91	N	RIGHT
013	BETTER	30/05/1982	24	F	CAUCASIAN	18.5	0.76	Y	RIGHT
014	BETTER	09/06/1986	20	F	CAUCASIAN	24.8	0.80	N	RIGHT
015	BETTER	03/09/1983	23	M	CAUCASIAN	21.8	0.80	N	LEFT
016	BETTER	08/08/1982	24	F	CAUCASIAN	33.0	0.83	N	RIGHT
017	POORER	26/02/1987	20	M	CAUCASIAN	23.0	0.84	N	LEFT
018	POORER	05/07/1983	23	F	CAUCASIAN	18.6	0.78	Y	RIGHT
019	POORER	05/10/1983	23	F	CAUCASIAN	19.8	0.79	N	RIGHT
020	BETTER	31/05/1986	20	M	CAUCASIAN	22.6	0.84	N	RIGHT

Appendix 1.3 Chapter 4 Participant Characteristics

PARTICIPANT NO.	TREATMENT	EFFORT	GLUCO-REGULATION	DOB	AGE	SEX	ETHNICITY	BMI	WHR	GLASSES	HANDEDNESS	YEARS IN EDUCATION	SMOKER (Per Day if Yes)
001	PLACEBO	HIGH	BETTER	04/02/1983	24	M	CAUCASIAN	25.6	0.90	Y	RIGHT	17	N
002	GLUCOSE	LOW	POORER	19/04/1985	22	M	ORIENTAL	19.1	0.84	Y	RIGHT	15	N
003	GLUCOSE	HIGH	POORER	09/10/1982	24	F	CAUCASIAN	20.8	0.76	Y	RIGHT	19	N
004	PLACEBO	LOW	BETTER	03/04/1986	21	F	CAUCASIAN	19.8	0.81	Y	RIGHT	17	N
005	PLACEBO	HIGH	BETTER	20/12/1974	33	M	CAUCASIAN	26.7	0.93	Y	RIGHT	16	N
006	PLACEBO	LOW	POORER	19/01/1980	27	F	CAUCASIAN	21.4	0.72	N	RIGHT	19	N
007	GLUCOSE	LOW	POORER	26/02/1987	20	M	CAUCASIAN	23.3	0.86	N	LEFT	15	N
009	PLACEBO	HIGH	BETTER	07/10/1984	22	M	CAUCASIAN	24.3	0.79	N	RIGHT	15	N
010	GLUCOSE	HIGH	POORER	05/04/1986	21	F	CAUCASIAN	19.6	0.74	N	RIGHT	16	N
011	PLACEBO	LOW	POORER	05/04/1986	21	F	CAUCASIAN	27.2	0.90	N	LEFT	16	N
012	GLUCOSE	LOW	BETTER	26/07/1986	20	M	CAUCASIAN	21.4	0.91	N	RIGHT	15	Y (10)
013	PLACEBO	HIGH	BETTER	18/04/1987	20	F	CAUCASIAN	26.4	0.85	N	RIGHT	15	N
014	GLUCOSE	HIGH	BETTER	15/07/1986	20	F	CAUCASIAN	19.8	0.82	N	RIGHT	16	N
015	GLUCOSE	LOW	BETTER	12/07/1984	22	F	CAUCASIAN	20.6	0.81	N	RIGHT	15	N
016	PLACEBO	HIGH	BETTER	28/08/1986	20	F	CAUCASIAN	22.3	0.81	N	RIGHT	17	N
017	PLACEBO	HIGH	POORER	08/01/1985	22	M	CAUCASIAN	21.3	0.83	N	RIGHT	18	N
018	GLUCOSE	LOW	POORER	20/06/1985	22	F	CAUCASIAN	24.8	0.82	N	RIGHT	16	Y (12)
019	PLACEBO	LOW	BETTER	31/03/1986	21	M	CAUCASIAN	25.2	0.85	N	RIGHT	16	N
020	GLUCOSE	HIGH	BETTER	20/05/1983	24	F	CAUCASIAN	19.7	0.81	N	RIGHT	17	N
021	PLACEBO	LOW	POORER	19/02/1985	22	M	CAUCASIAN	26.0	0.87	N	RIGHT	17	N
022	PLACEBO	LOW	BETTER	23/10/1983	23	F	CAUCASIAN	19.8	0.79	Y	RIGHT	16	N
023	GLUCOSE	HIGH	BETTER	28/08/1985	22	F	ORIENTAL	20.3	0.83	N	RIGHT	16	N
025	PLACEBO	LOW	POORER	28/06/1985	22	F	CAUCASIAN	20.7	0.83	N	RIGHT	16	N
026	PLACEBO	HIGH	BETTER	04/05/1985	22	M	CAUCASIAN	28.1	0.88	N	RIGHT	17	N
027	GLUCOSE	HIGH	POORER	18/06/1986	21	F	CAUCASIAN	30.5	0.90	N	RIGHT	16	N
028	GLUCOSE	LOW	POORER	09/08/1986	20	F	CAUCASIAN	26.8	0.88	N	RIGHT	16	Y (7)
029	PLACEBO	LOW	POORER	28/06/1985	22	F	CAUCASIAN	22.0	0.82	N	RIGHT	16	N
030	PLACEBO	HIGH	BETTER	18/07/1972	34	F	CAUCASIAN	27.9	0.86	N	RIGHT	23	N
032	GLUCOSE	HIGH	POORER	04/11/1985	21	F	CAUCASIAN	19.1	0.78	N	RIGHT	16	N
033	PLACEBO	LOW	BETTER	23/03/1987	20	F	CAUCASIAN	25.8	0.79	N	RIGHT	15	N
034	GLUCOSE	HIGH	BETTER	09/12/1986	20	M	CAUCASIAN	21.3	0.91	N	RIGHT	15	Y (2)
035	PLACEBO	HIGH	BETTER	29/09/1984	22	F	CAUCASIAN	24.3	0.87	N	RIGHT	16	N
036	GLUCOSE	LOW	POORER	14/02/1985	22	M	CAUCASIAN	25.3	0.89	N	RIGHT	16	N
037	PLACEBO	LOW	POORER	01/11/1986	20	F	ASIAN	26.4	0.79	Y	RIGHT	15	N
039	GLUCOSE	LOW	POORER	03/08/1973	33	M	CAUCASIAN	23.7	0.94	N	RIGHT	16	N
040	PLACEBO	HIGH	POORER	09/05/1981	26	M	CAUCASIAN	26.6	0.98	N	RIGHT	11	N
042	GLUCOSE	LOW	POORER	24/03/1986	21	F	CAUCASIAN	33.5	0.91	Y	RIGHT	16	Y (12)
043	PLACEBO	HIGH	POORER	14/09/1986	20	F	CAUCASIAN	26.3	0.82	N	RIGHT	15	N
044	GLUCOSE	HIGH	POORER	23/10/1981	25	M	CAUCASIAN	20.5	0.80	Y	RIGHT	15	N
045	PLACEBO	LOW	BETTER	21/05/1986	21	F	CAUCASIAN	21.6	0.81	N	RIGHT	16	N
046	GLUCOSE	LOW	BETTER	11/03/1982	25	M	CAUCASIAN	22.4	0.83	Y	RIGHT	20	N
047	GLUCOSE	HIGH	POORER	16/06/1986	21	F	CAUCASIAN	19.9	0.81	N	RIGHT	16	N
049	GLUCOSE	HIGH	BETTER	13/12/1973	33	M	BLACK	20.8	0.83	N	RIGHT	22	N
050	PLACEBO	HIGH	BETTER	16/11/1983	23	F	CAUCASIAN	27.3	0.86	N	RIGHT	18	N
051	PLACEBO	LOW	POORER	21/03/1985	22	M	CAUCASIAN	23.0	0.85	Y	RIGHT	17	N
053	GLUCOSE	HIGH	POORER	20/10/1985	22	M	CAUCASIAN	24.6	0.90	N	RIGHT	15	Y (5)
054	PLACEBO	HIGH	BETTER	14/04/1988	19	M	CAUCASIAN	22.2	0.88	N	LEFT	14	N
055	GLUCOSE	LOW	BETTER	08/07/1985	22	M	CAUCASIAN	17.9	0.78	N	RIGHT	17	N
056	PLACEBO	LOW	BETTER	22/02/1989	18	F	CAUCASIAN	23.3	0.83	Y	LEFT	14	N
057	GLUCOSE	HIGH	BETTER	06/04/1988	19	M	BLACK	23.7	0.84	N	RIGHT	14	N
058	PLACEBO	LOW	POORER	25/09/1987	20	M	CAUCASIAN	26.2	0.91	N	LEFT	15	N
059	PLACEBO	HIGH	BETTER	29/07/1989	18	F	CAUCASIAN	20.6	0.85	N	RIGHT	13	N
060	GLUCOSE	LOW	POORER	14/01/1981	26	M	CAUCASIAN	27.8	0.89	N	RIGHT	18	N
061	GLUCOSE	HIGH	POORER	22/12/1988	18	M	CAUCASIAN	26.8	0.85	N	RIGHT	14	N
062	PLACEBO	LOW	BETTER	26/06/1987	20	F	CAUCASIAN	23.1	0.73	Y	RIGHT	16	N
063	GLUCOSE	LOW	POORER	26/07/1988	19	M	CAUCASIAN	23.9	0.79	N	RIGHT	14	N
064	GLUCOSE	LOW	BETTER	01/07/1989	18	M	CAUCASIAN	22.6	0.83	N	RIGHT	14	N
065	GLUCOSE	LOW	BETTER	16/07/1985	22	M	BLACK	23.9	0.80	N	RIGHT	16	N
066	PLACEBO	HIGH	POORER	23/01/1987	20	F	CAUCASIAN	20.9	0.80	N	RIGHT	16	N
067	GLUCOSE	HIGH	POORER	14/03/1982	25	F	CAUCASIAN	24.1	0.84	N	RIGHT	18	Y (12)

Appendix 1.4 Chapter 5 Participant Characteristics

PARTICIPANT NO.	GLUCO-REGULATION	DOB	AGE	SEX	ETHNICITY	BMI	WHR	GLASSES	HANDEDNESS	YEARS IN EDUCATION
001	BETTER	25/8/1988	19	M	CAUCASIAN	23.4	0.88	N	RIGHT	15
002	BETTER	05/9/1984	23	M	CAUCASIAN	21.8	0.79	N	RIGHT	17
003	BETTER	28/3/1983	25	M	CAUCASIAN	28.2	0.93	N	RIGHT	19
004	BETTER	10/3/1985	23	M	CAUCASIAN	24.7	0.86	N	RIGHT	18
005	POORER	27/9/1985	22	M	ASIAN	20.2	-	N	RIGHT	13
006	BETTER	25/12/1985	22	M	BRITISH INDIAN	31.1	-	N	RIGHT	18
007	BETTER	25/12/1986	21	M	CAUCASIAN	25.1	0.90	Y	RIGHT	12
008	BETTER	17/9/1979	29	M	MIXED	22.7	0.93	N	RIGHT	17
009	POORER	22/6/1984	24	M	CAUCASIAN	19.6	0.77	Y	LEFT	18
010	POORER	27/8/1974	33	M	CAUCASIAN	22.4	0.86	Y	RIGHT	16
011	POORER	16/04/1989	19	F	CAUCASIAN	27.6	0.83	N	RIGHT	14
012	BETTER	11/11/1975	32	F	CAUCASIAN	22.3	0.82	N	RIGHT	16
013	BETTER	10/05/1982	26	F	CAUCASIAN	23.9	0.80	N	RIGHT	19
014	BETTER	10/7/1983	25	F	CAUCASIAN	22.1	0.87	N	RIGHT	19
015	BETTER	05/02/1988	20	M	CAUCASIAN	26.3	0.87	N	RIGHT	16
016	BETTER	27/10/1983	24	F	CAUCASIAN	51.7	0.83	N	RIGHT	18
017	POORER	19/6/1979	29	F	CAUCASIAN	21.5	0.79	N	RIGHT	18
018	POORER	30/5/1983	26	F	CAUCASIAN	18.3	-	Y	RIGHT	18
019	POORER	15/03/1981	27	F	CAUCASIAN	22.5	0.80	Y	RIGHT	19
020	POORER	28/1/1988	20	F	CAUCASIAN	19.4	0.75	N	RIGHT	15
021	POORER	23/04/1988	20	F	CAUCASIAN	21.4	0.86	N	LEFT	15
022	POORER	02/08/1989	19	F	CAUCASIAN	20.9	0.80	N	RIGHT	14

Appendix 1.5 Chapter 6 Participant Characteristics

PARTICIPANT NO.	GLUCO-REGULATION	DOB	AGE	SEX	ETHNICITY	BMI	WHR	GLASSES	HANDEDNESS	YEARS IN EDUCATION
001	POORER	28/3/84	25	M	MIXED	19.2	0.85	N	RIGHT	13
002	BETTER	10/8/84	24	M	ASIAN	24.4	0.85	N	RIGHT	13
003	BETTER	1/5/90	19	F	CAUCASIAN	22.0	0.78	Y	RIGHT	14
004	BETTER	9/5/82	27	M	CAUCASIAN	25.0	0.84	Y	RIGHT	18
005	POORER	25/11/87	21	M	CAUCASIAN	19.3	0.82	Y	RIGHT	16
006	BETTER	15/9/88	20	M	CAUCASIAN	23.7	0.85	N	RIGHT	15
007	BETTER	4/2/77	32	F	CAUCASIAN	27.8	0.70	N	RIGHT	14
008	BETTER	1/5/90	19	M	CAUCASIAN	21.6	0.90	Y	LEFT	13
009	POORER	15/5/85	24	F	CAUCASIAN	20.8	0.87	Y	RIGHT	16
010	POORER	19/1/80	29	F	CAUCASIAN	22.4	0.72	N	RIGHT	20
011	POORER	24/2/89	20	F	CAUCASIAN	19.7	0.82	N	RIGHT	15
012	POORER	11/11/75	33	F	CAUCASIAN	23.3	0.77	N	RIGHT	16
013	BETTER	31/10/89	19	F	CAUCASIAN	19.0	0.70	N	RIGHT	14
014	POORER	28/8/74	34	M	CAUCASIAN	30.3	0.83	N	RIGHT	17
015	POORER	19/12/89	20	F	ASIAN	18.8	0.78	N	RIGHT	14
016	BETTER	17/8/89	19	M	CAUCASIAN	26.5	0.87	N	RIGHT	14
017	BETTER	19/12/89	19	F	CAUCASIAN	34.2	0.86	Y	RIGHT	14
018	BETTER	5/11/83	25	M	CAUCASIAN	23.4	0.84	N	RIGHT	18
019	POORER	10/6/87	22	M	CAUCASIAN	32.4	0.94	N	RIGHT	17
020	POORER	6/6/81	28	F	CAUCASIAN	18.2	0.78	N	RIGHT	18

APPENDIX 2. Number Search Task

Please circle each pair of even numbers in a row going across the page from left to right. For example 3 (6 4) 5 8 7 4 5 (6 8) 5 4 7 2 1 7 4 9 3 (2 4) 3 9 8 1 6 5 4 5 9 7 2

6 3 5 3 1 1 6 4 3 5 4 8 3 4 1 2 7 1 3 1 2 8 5 8 1 8 2 1 7 2 5 9 6 2 7 2 9 9 8 3
1 8 7 6 7 9 9 4 8 3 1 2 8 1 5 2 5 7 1 2 1 5 6 9 6 7 6 3 9 6 4 7 7 4 5 4 7 4 6 9
1 4 1 1 3 3 1 3 9 6 1 2 7 5 4 9 6 9 8 2 9 2 8 3 4 5 2 1 7 6 8 1 7 5 1 8 7 4 1 1
7 1 9 7 1 5 3 6 8 7 7 6 3 8 9 8 3 9 7 4 5 3 7 4 5 6 5 6 3 5 7 4 7 8 2 3 4 9 3 4
6 1 2 6 1 5 3 8 3 7 9 1 8 9 2 9 8 8 7 3 8 9 1 9 2 7 5 7 5 9 8 1 6 6 3 6 7 3 8 2
4 9 2 5 1 2 3 4 6 1 3 4 9 3 2 6 7 6 3 8 5 8 7 2 4 1 2 3 2 1 5 8 5 2 5 3 8 8 3 6
1 8 6 5 1 7 7 7 6 1 7 8 2 9 4 3 9 3 5 6 7 3 1 5 7 6 9 7 9 3 3 1 6 1 7 9 5 3 6 7
3 7 6 1 7 8 4 3 5 9 7 6 9 6 7 1 9 2 3 6 1 4 6 9 1 5 3 7 9 9 2 8 7 3 7 4 3 2 4 3
8 5 5 1 9 1 7 8 9 5 9 9 4 5 1 3 8 2 9 1 6 2 3 4 2 5 1 1 2 2 3 9 9 1 2 4 7 3 9 4
9 4 9 4 8 5 3 8 1 4 5 7 4 2 5 2 9 1 7 7 4 2 7 4 1 5 9 9 7 8 9 1 2 6 1 3 1 4 4 1
6 7 1 1 9 8 7 7 9 5 4 7 8 9 2 6 5 6 9 9 4 3 6 2 5 7 2 1 1 3 1 9 7 1 2 1 5 9 2 4
3 8 2 9 8 1 7 9 3 8 7 6 3 2 1 5 9 4 2 5 7 4 9 9 2 8 7 5 9 4 7 9 5 2 9 6 4 9 6 9

8 2 7 7 6 6 1 6 7 7 9 1 6 8 9 3 1 4 9 2 3 9 8 9 7 8 1 2 9 8 9 9 5 5 5 6 3 5 7 2
3 9 4 7 2 9 5 9 6 5 8 6 9 3 3 8 3 3 4 4 3 9 7 4 3 9 2 1 5 4 2 7 3 9 6 4 9 3 5 3
6 4 1 2 3 9 3 8 2 7 4 1 2 9 8 4 1 9 9 5 8 6 1 4 7 3 2 7 8 7 4 3 4 5 7 4 8 7 3 5
5 5 3 7 2 1 7 3 4 3 2 2 7 2 5 6 4 9 7 1 5 9 2 3 1 6 2 9 7 2 9 4 7 5 4 6 7 1 3 8
8 7 8 4 3 4 2 1 9 7 9 8 3 3 9 4 7 2 7 2 4 1 4 1 9 1 5 3 9 4 3 4 2 9 3 7 6 8 9 3
7 1 9 1 4 6 3 5 4 4 9 9 7 7 6 3 4 1 4 1 1 4 9 8 2 1 1 3 5 3 6 7 6 5 7 6 6 1 1 6
8 6 3 7 9 5 8 3 1 9 3 8 5 3 3 3 1 2 9 2 4 7 6 9 1 8 1 4 2 3 4 3 6 8 3 6 1 7 2 8
5 9 2 7 6 1 4 9 4 7 6 8 7 5 4 2 5 6 5 9 7 7 2 5 7 6 4 1 5 3 1 7 3 4 8 1 7 5 6 1
7 4 3 5 8 4 5 7 1 8 1 6 1 5 5 6 9 9 7 5 3 1 1 9 2 9 5 6 3 1 6 7 5 3 6 5 2 4 5 9
5 4 2 7 2 3 3 7 3 2 7 8 3 4 9 2 3 1 7 7 3 4 8 5 6 2 7 8 3 1 8 9 6 5 9 9 9 8 4 3
3 7 9 3 6 1 7 5 2 1 6 9 7 3 7 9 4 3 9 5 6 4 9 2 3 3 5 8 5 3 8 6 7 1 5 8 7 4 5 6
1 1 6 7 1 1 8 1 7 4 8 1 8 3 4 3 8 7 1 1 6 2 5 3 6 3 7 8 7 3 7 4 1 3 6 8 7 4 3 9

APPENDIX 3. Food Diary Sheets

Appendix 3.1 Chapter 2 Food Diary Sheet

Screening Number:_____

17f1 Food & Drink Diary Sheet

Next Test Visit: / / 8.30 am

Please fill out this food and drink diary for ***the day before you come in*** for your next university visit. Please be as precise as possible!

Please remember not to eat after 10pm on the night before your next visit and DO NOT eat breakfast on the morning before you come back to the university. You are only allowed to drink water. Thank You!

1. What did you eat for breakfast?

   _____
   _____
   _____

2. What did you eat for lunch?

   _____
   _____
   _____

3. What did you eat for you evening meal? What time did you eat this?

   _____
   _____
   _____

4. Did you eat any snacks? If yes, what snacks?

   _____
   _____
   _____

5. What drinks did you have? e.g. a pint of water, a cup of tea, a can of lemonade....

   _____
   _____
   _____

6. What time did you last eat anything today?

   _____
   _____
   _____

7. What time did you last drink anything other than water?

   _____
   _____
   _____

Appendix 3.2 Chapters 3, 4 and 5 Food Diary Sheet

Food & Drink Diary

Study Visit # **Date:** / / .

Please fill out this food and drink diary for the day before you come into the lab for your study visit. Please try to eat the same evening meal as you did prior to coming in for your first visit and also to fast for 12hours before you come into the lab, drinking only water.

1. What did you eat for breakfast?

   _____
   _____
   _____

2. What have you eaten for lunch?

   _____
   _____
   _____

3. What did you eat for dinner? What time did you have dinner?

   _____
   _____
   _____

4. Have you eaten any snacks today? If yes, what snacks?

   _____
   _____
   _____

5. What drinks have you consumed? Please give quantities e.g. a pint of water, a small cup of ……..

   _____
   _____
   _____

6. What time did you last eat anything today?

   _____
   _____
   _____

7. What time did you last drink anything other than water?

   _____
   _____
   _____

8. ***COMPLETE IN LAB*** What have you drunk so far today? Please give quantities e.g. a pint of water, a small cup of ……..

   _____
   _____
   _____

9. What time did you get up today? _____

APPENDIX 4. Short Form State Trait Anxiety Inventory (SF STAI)

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the most appropriate number to the right of the statement to indicate **how you feel right now, at this moment**. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	Not at all	Somewhat	Moderately	Very much
1. I feel calm ……..…	1	2	3	4
2. I feel tense ..……	1	2	3	4
3. I am upset …...……	1	2	3	4
4. I feel relaxed …..……	1	2	3	4
5. I feel content ……..……	1	2	3	4
6. I am worried ……...	1	2	3	4

Please make sure you have answered *all* the questions.

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