The Impact of Elevated Risk of Poor Glucoregulation on Cognition: Comparing Neurophysiological, Glucoregulatory and Cardiovascular Factors in Non-diabetic Healthy Young Adults Vs Non-Diabetic, Potentially At-Risk Young Adults.

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Dedication

“I think, at a child's birth, if a mother could ask a fairy godmother to endow it with the most useful gift, that gift would be curiosity”.

Eleanor Roosevelt

To my late father Harry Bonner, who taught me how to be curious.

Abstract

The global prevalence of metabolic syndrome, which is predominantly characterised by insulin resistance and is a precursor to type two diabetes mellitus (T2DM), is a major health concern. In 2018 it was estimated that 1 in 3 older adults aged 50 or over in the UK were affected by metabolic syndrome. The global prevalence of type two diabetes mellitus (T2DM), and its co-presenting cognitive impairment, is alarming. With 171 million afflicted individuals in 2000 and expectations that this will rise to 366 million, by the year 2037. Known risk factors for the development of T2DM, are obesity, poor glucoregulatory control, normal ageing, high-blood pressure, smoking, physical inactivity, and other negative lifestyle choices such as an unhealthy high carbohydrate diet.

Using a novel combination of methodologies, this thesis aimed to validate theories of memory recognition and glucose enhancement effects to achieve an understanding of the mechanisms involved in memory impairment, often co-morbid with T2DM. Glucose and glucoregulation have been shown to mediate cognitive functioning, although inconsistent results are reported. Chapters 2 and 3 investigated whether these anomalies may be a result of differential treatment ingredients being used by research centres, with a view to establishing best practice for experimental and placebo treatment composition. Some ingredients were not cognitively inert, potentially suggesting some inconsistencies in the glucose enhancement literature may be influenced by treatment ingredients rather than a direct glucose effect.

Chapters 4 and 5 explored the impact of glucose ingestion and early sub-clinical deficits in glucoregulatory control, on episodic memory in young, non-diabetic adults. EEG was used and nuanced memory differences were indeed visible in this population, offering important insight into early cognitive and structural changes underpinning glucoregulation linked cognitive decline. Also investigated, was cardiovascular health which is implicated in T2DM. Ingested glucose accelerated heart rate for both better and poorer regulators, and although only a trend, poorer regulators had globally higher heart rate than better regulators. Chapter 5 explored the potential of a questionnaire, based on known T2DM risk factors alongside glucoregulation measures, as a means of identifying a T2DM risk profile. This section provided evidence suggesting that these known associable T2DM risk factors have a significant positive relationship with blood glucose measures (iAUC) taken via an oral glucose tolerance test. Heart rate variability, which is also implicated in T2DM, was also found to be correlated with T2DM risk scores, blood glucose levels, and baseline heart rate, with more widespread effects being seen in poorer glucoregulators. As these effects have been observed in this

population, the relationship between these measures provides evidence for the efficacy of this risk assessment model as a preventative intervention which could lead to lifestyle changes being put into place prior to the onset of T2DM.

Further exploration of the methodologies employed here, comparing populations of different age-groups and pathologies, would help to gain further knowledge of the mechanistic pathways which mediate memory impairment, and give more insight into cognitive decrements associated with impaired glucoregulatory control and T2DM.

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Finally, to my lovely family for their love and support, this has meant so much more than I can say.

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.

Name: Angela Bonner

Signature: 

Date: 3rd of February 2022

1 Introduction

1.1 General Introduction

It is well known that the human brain, despite weighing approximately 2% of the body weight of an average adult, accounts for around 20% of the body's resting metabolic rate. Glucose is the primary source of energy to the brain and because there is a limited capacity to store this energy, the process of circulatory glucose crossing the blood-brain barrier is intrinsically linked to cognitive functioning. The limited capacity for storage of glucose-derived energy, only suffices to satisfy cognitive demand for circa 10 minutes (Marks & Rose, 1981). The failure to provide a continuous supply of this energy leads to cognitive impairment and ultimately death.

1.2 Glucose Metabolism and Homeostasis

As the brain is almost entirely reliant on circulatory blood glucose as its primary energy source, glucose homeostasis must be tightly controlled to regulate the transport, and subsequent metabolism of glucose in the brain. The insulin signalling pathway is essential to regulating the concentration of glucose in the blood following a carbohydrate rich meal. This pathway consists of many steps, and failure of any of these steps can have severe consequences for glucoregulatory control. Type 1 diabetes, a metabolic autoimmune disease, occurs because the immune system attacks the insulin producing beta cells. The prevention of insulin synthesis, the process which converts excess glucose to glycogen, results in excessively high blood glucose levels. Differentially, Type 2 diabetes mellitus (T2DM) occurs when insulin receptors no longer respond to insulin, again resulting in elevated blood glucose levels.

Secretion of the pancreatic hormones insulin and glucagon play a key role in the maintenance of glucose homeostasis, see **Figure** 1.1 for a schematic of this process. During the absorptive phase of food consumption, glucose is released into the bloodstream post digestion. This release of glucose stimulates the release of insulin from the pancreas, and this stimulates glycogen synthesis in the liver (glycogenesis). The conversion of glucose to glycogen facilitates the storage and subsequent later release of glucose, a process known as glycogenolysis, during fasting periods and following exercise. For a male of average weight, the available energy provided by stored glucose would be in the region of 40 kcal, whereas glycogen provides an accessible form of stored glucose of around 600 kcal, which

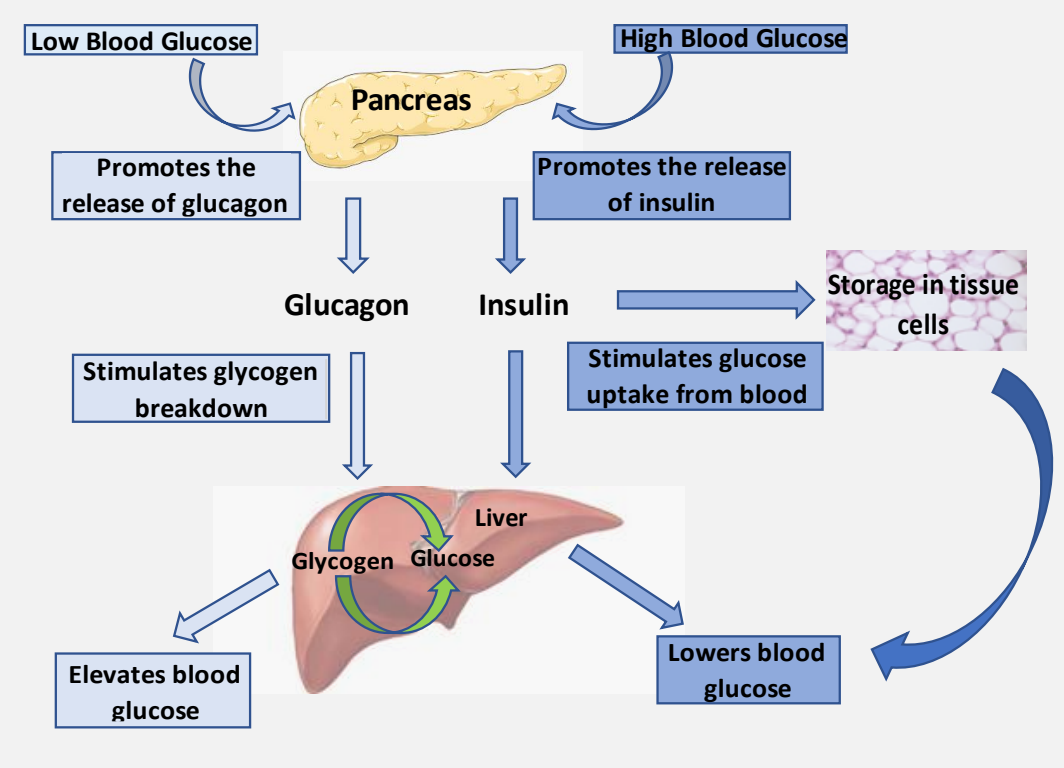
is still maintained after fasting overnight. Following a sustained fast of more than circa 8 hours, gluconeogenesis, which synthesises glucose from other non-carbohydrate substrates such as lactate, alanine, and glycerol, begins to replace glycogenolysis. This change preserves glycogen stores and after a ten hour fasting period only 70% of glucose production is accounted for by glycogenolysis (Tirone & Brunicardi, 2001). Glycogen reserves are exhausted following approximately 20 hours of fasting, after which gluconeogenesis increases to the extent that, after circa 72 hours, glucose production by the liver is almost exclusively the result of gluconeogenesis.

Whilst rising blood glucose levels stimulate the release of insulin, the hormone glucagon has an opposing effect, with the pancreas being stimulated to release glucagon when blood glucose levels are falling. Gluconeogenesis is stimulated by glucagon and inhibited by insulin and is to a large extent dependent on the breakdown of muscle protein. Approximately 1.75 g of muscle is converted to 1 g of glucose which equates to 150 g of protein per day used to provide the brain with sufficient glucose. To spare protein stores and prevent excessive muscle breakdown, a further adaptation is initiated; via a process called ketogenesis, in which the liver converts fatty acids into ketone bodies which can then be used by peripheral tissue as an energy source. Following starvation for 1 or 2 days, ketone bodies will become an energy source for the brain, reducing the need for glucose synthesis with up to 50% of energy required by the brain being sourced from ketone bodies.

1.2.1 The Role of Insulin in Peripheral Glucose Homeostasis

The function of the hormone insulin is to extract circulating glucose from the blood and synthesize it into glycogen, via a process called glycogenesis, which then enables it to be stored in the cells as fuel for future energy requirements (see section 1.2 for a more detailed account). The efficient secretion of insulin by the islets of Langerhans in the pancreas is crucial in the management of peripheral glucose homeostasis. A symbiotic relationship between blood glucose and insulin release is critical to maintaining healthy levels of homeostatic control.

Figure **1.1 The roles of the pancreatic hormones insulin and glucagon in the peripheral homeostatic control of blood glucose, ensuring that blood glucose concentrations are tightly regulated.**



Efficient glucose regulation is maintained by the compensatory release of insulin by β cells located in the pancreas. When efficient insulin sensitivity is present, normally functioning β cells release this compensatory insulin to maintain glucose homeostasis. However, dysfunctional β cells failing to release sufficient insulin, results in rising glucose levels and then hyperglycaemia (Awad et al., 2004; Biessels & Reagan, 2015; Cerf, 2013; Kahn et al., 2014). Homeostatic levels of circulatory blood glucose are augmented by healthy glucoregulation, whereas poor or impaired glucoregulation fails to maintain these optimum levels (Lamport et al., 2009).

Insulin resistance is developed when cells fail to respond normally to insulin. There is increasing evidence in the literature that supports the notion that insulin resistance plays a significant part in the origin and development of cognitive impairment and neurodegeneration, with insulin playing an important role in cognitive functionality (for a review see Ma et al., 2015). Sub-optimal insulin signalling in the brain may be a contributing factor to cognitive damage, which is a precursor of dementia (Cetinkalp et al., 2014).

1.2.2 The Role of Insulin in Cerebral Glucose Homeostasis

The metabolism of glucose is the principal source of energy for the brain, and brain tissue is initially solely reliant on the oxidative metabolism of glucose for energy (see section 1.2 for a more detailed account of cerebral energy sources). The brains vast energy requirement, relative to brain weight and volume, is due to the needs of billions of neuronal cells which are active 24 hours per day. As the brain does not store excess energy, its continuous energy requirements rely on a constant supply of oxygen and glucose. In the event of a loss of oxygen and blood to the brain, an individual would lose consciousness within 5 – 10 seconds and following a period of deprivation for several minutes, permanent damage to the brain would ensue. Similarly, deprivation of glucose alone is just as destructive, such as in hypoglycaemia, but this would occur after a longer time lapse of approximately 6 hours after the consumption of a meal as other substrates can be used (see section 1.2).

Glucose is transported across the blood brain barrier (BBB) by a group of glucose (GLUT) transporters, each of which are customised to meet the metabolic requirements of the tissue in which the glucose is found. The principal GLUT transporters supplying the brain are the GLUT-1 and GLUT-3 (Benton, 2005). On entering brain cells, glucose is converted to pyruvate in the glycolytic pathway. The pyruvate is then metabolised through the Krebs cycle, which is the aerobic pathway of glucose and carbohydrate metabolism, to generate adenosine triphosphate (ATP) which is the principal carrier of chemical energy. Recent research suggests that the insulin sensitive GLUT-4 glucose transporter has a crucial role in hippocampal memory processes, with reductions in activity of GLUT-4 potentially underpinning cognitive impairments which have resulted from insulin intolerance (McNay & Pearson-Leary, 2020).

In terms of cerebral glucose metabolism, the principal purpose of insulin is the removal of blood glucose via GLUT-4 glucose transporters from intracellular sites such as, the heart, adipose tissue, and skeletal muscle. The GLUT-4 then travel to the surface of the membrane and facilitate an increase of glucose in the plasma membrane which can then be absorbed into the brain for use when needed. GLUT-4 is highly expressed in the hippocampus where there is an abundance of insulin receptors; the regulation of GLUT-4 is a potential mechanism by which insulin mediates hippocampal cognition.

Throughout adult life the hippocampus generates new neurons (neurogenesis) (Braun & Jessberger, 2014). There is a growing body of research which supports the notion that hippocampal neurogenesis has a crucial role in learning and memory and suggests that impairment of this process can be linked with cognitive dysfunction and neurodegenerative disorders such as Alzheimer's disease (Taylor et al., 2013). A further threat to learning and memory is a high-fat diet which has been shown to impair insulin signalling in the hippocampus (Arnold et al., 2014). For several decades, the dietary advice given to individuals with glucoregulatory disorders such as T2DM, was to follow the public health advice of a diet low in fat and high in unrefined carbohydrate (for a systematic review and meta-analysis see Snorgaard et al., 2017). However, more recent evidence is emerging which suggests that the restriction of carbohydrate per se, alongside higher consumption of protein and unsaturated fat confer greater benefits in terms of improving glycaemic control. A two year clinical trial examined energy-restricted low carbohydrate, with both low and high saturated fat, diet versus the traditional high-carbohydrate/low fat diet in T2DM individuals (Tay et al., 2018); it was found that whilst both the low and high carbohydrate interventions achieved similar weight loss, the low carbohydrate option also improved glycaemic control and reduced the need for diabetes medication. These findings may be considered to be commensurate with the notion that insulin tolerance is challenged by the increased glycaemic load of the habitual consumption of high carbohydrate foods, potentially leading to insulin resistance.

Defective insulin signalling has been linked to impaired neurogenesis (Lindqvist et al., 2006) and impairments in hippocampal synaptic plasticity (for a review see Spinelli et al., 2017). Brain insulin resistance impairs the ability of neuronal cells in the brain to respond to insulin, impairing metabolic and cognitive effects that would be derived from the hormone (for a review see Kullmann et al., 2016).

1.2.3 Glucose Tolerance

Glucose tolerance may be defined as the capacity to effectively metabolise an ingested glucose load. Efficient glucose tolerance is maintained by the compensatory release of insulin. When functioning normally insulin serves to maintain glucose homeostasis (see section 1.2.1 above for a more detailed account). The gold standard assessment of glucose tolerance is via an oral glucose tolerance test (OGTT) in which a 75 g glucose dose is administered following a 12 hour overnight fast (water permitted). Circulatory blood glucose levels are measured at baseline and then at 30-, 60-, 90- & 120-minutes post glucose load. In healthy individuals blood glucose levels will rise post dose but will

be brought back to near normal levels by the 120-minute blood test. Elevated blood glucose after the same period is indicative of impairment. The diagnostic levels of glucose tolerance can be seen below in Table 1.1, these are shown in relation to the 12 hour fasting time-point as well as two hours post consumption of the 75 g glucose load.

Table 1.1 OGTT plasma glucose test diagnostic levels of normal, pre-diabetic, and diabetic glucose tolerance assessed after a twelve hour fast and at two hours post glucose load.

Test taken	Normal	Pre-diabetes 'impaired glucose tolerance'	Diabetes
12 hour fasting	Below 6 mmol/L	6.0 to 7.0 mmol/L	Over 7.0 mmol/L
2 h post glucose load	Under 7.8 mmol/L	7.9 to 11.0 mmol/L	Over 11.0 mmol/L

Insulin resistance results in β cells failing to release sufficient insulin, leading to rising glucose levels and then hyperglycaemia (for a review see Biessels & Reagan, 2015; Cerf, 2013; Kahn, et al., 2014) (see section 1.2.1 and section 1.2.2 for a more in depth discussion of the role of insulin). Impaired glucose tolerance is diagnosed when blood glucose levels are raised beyond normal levels, but not high enough for a diabetes diagnosis. Impaired glucose tolerance increases the risk of developing T2DM diabetes and cardiovascular disease (CVD) (Wilson et al., 2005).

1.2.4 Hypoglycaemia

As the brain is reliant (almost entirely) on continuous delivery of blood glucose, the brain and cognition are vulnerable to damage should hypoglycaemia (low blood glucose) occur. Symptoms include trembling, dizziness, accelerated heartbeat, poor concentration, confusion, sweating and mood changes. Hypoglycaemia occurs when glucose levels fall below 4.0 mmol/L. The small amount of glycogen that is stored in the brain, is found almost entirely in the glial cells and the metabolism of glycogen is utilised to support the metabolic requirements of the glial cells rather than neuronal demands (Swanson, 1992). This limited amount of glycogen would sustain brain function for circa 3 minutes.

Acute hypoglycaemia challenges efficient cognitive function, manifesting as impaired awareness, confusion and concentration difficulties (Heller & Novodvorsky, 2019), with prolonged hypoglycaemia ultimately leading to loss of consciousness and even death (for a review see Warren & Frier, 2005). When hypoglycaemia is present responses occurring in the brain may include the

central sympathetic nervous system being activated, variations in cognitive function, notably concentration difficulties and drowsiness (Barbagallo, 2014). The hippocampus, which has a strong relationship with memory processes, is extremely vulnerable to damage caused by hypoglycaemia (Lamport et al., 2009), see section **Error! Reference source not found.** for a more detailed description of the hippocampus.

1.3 Conditions which Increase Risk for Poor Glucoregulation

1.3.1 Normal Ageing

Declining glucose tolerance and insulin sensitivity can be a consequence of normal aging. The mechanisms for this are as yet unclear, and there is mixed reporting of the causality of these decrements. Some research suggests that impaired glucose tolerance in the elderly may be influenced by, or related to other elements, such as increases in visceral fat (Gabriely et al., 2002), smoking (Parchwani et al., 2013) or diminishing physical activity (Bowden Davies et al., 2019).

Despite differential research in terms of causality, the relationship between age and impaired glucoregulatory control is a potential explanation for age related memory impairment. A longitudinal study of 101 elderly adults (>75 years old), explored the potential risk for cognitive decline (Ravona-Springer et al., 2012). Participants were assessed by the mini mental state examination (MMSE), as being cognitively normal at baseline, with normal HbA1c (average blood glucose levels over the last two to three months) with follow up assessment of MMSE and HbA1c conducted annually over 3 years. Outcomes suggested, in this population of non-diabetic, non-demented elderly adults, that increased blood glucose levels over time was correlated with cognitive decline.

Evidence from neuroimaging studies has also brought into question whether age-related cognitive decrements are merely part of a normal aging process or, a function of negative lifestyle choices. At present, in a clinical setting, it is the normal procedure to assess cognition in older adults based purely on cognitive test scores without controlling for age and education. A magnetic resonance imaging (MRI) study can compare both whole brain and regional rates of cerebral glucose metabolism and insulin resistance. One study comparing younger and older cognitively-normal adults, sought to identify age-normalised levels of cerebral metabolic glucose (Nugent et al., 2016). The outcomes of this study would inform a base measure of valid reference values for normal healthy adults. Participants were assessed on the MMSE, executive function, processing speed, inhibition, working memory, and immediate and delayed episodic memory. The neurological

outcomes demonstrated that the metabolic phenotype of the older adults showed similar levels of plasma glucose and insulin when compared to the healthy young adults. Positron emission tomography revealed that lower rates of cerebral metabolic glucose were seen in the superior frontal cortex of older adults. However, no between age difference was found in the hippocampus and white matter. Cognitive scores were normal for the older age-group, which suggests that age-related metabolic changes do not always result in cognitive impairment. The authors suggest that metabolic-endocrine status should also be assessed to eliminate the confound of glucose intolerance in healthy adults.

Some potential influencers of neurocognitive aging include poor glucoregulatory control, oxidative stress, and inflammation which may be reversed by the inclusion of adequate nutrients which support healthy cognition, either as part of a healthy diet or via supplementation (Scholey, 2018). This nutritional approach to healthy neurological aging is commensurate with the scaffolding theory of aging and cognition (STAC) (Park & Reuter-Lorenz, 2009). This adaptive model suggests that cognitive aging can be ameliorated by the compensatory recruitment of additional neuronal circuitry which supports structures that are in decline. In the light of new structural evidence in the literature, the authors revised their original theory to include existence of 'positive' plasticity, such as neurogenesis, as opposed to just 'negative' plasticity which manifested in those adverse changes in brain structure which impact the aging brain (Reuter-Lorenz & Park, 2014). The revised model (STAC-r) suggests that this positive plasticity can be stimulated by continued intellectual engagement and new learning, along with interventions such as cognitive training and, it can also be supported by lifestyle choices such as exercise and healthy nutrition.

1.3.2 Metabolic Syndrome

The World Health Organisation (WHO) defines metabolic syndrome as a non-contagious pathological condition which has rapidly become the foremost threat to global health, to the extent that it is estimated that approximately one third of adults in the USA have metabolic syndrome. The condition is typified by the presence of abdominal obesity and insulin resistance, commonly accompanied by hypertension and hyperlipidaemia (Saklayen, 2018). This prevalence of metabolic syndrome is predominantly driven by the increasing consumption of highly calorific, low fibre, and highly processed fast food. This is exacerbated by reductions in physical activity brought about by an increase in more sedentary lifestyle choices. Metabolic syndrome, as a precursor of T2DM (Wilson et al., 2005), is associated with an increased potential to develop cognitive dysfunction in individuals

who have a poor metabolic profile. It has been suggested that if this association is causal, a significant number of dementia cases could potentially be prevented by efficient control of insulin homeostasis (Neergaard et al., 2017).

1.3.3 Obesity

Increased body mass is associated with insulin resistance and poor glucose tolerance. Plasma glucose concentration has been regarded as an effective predictor of T2DM. It is widely recognised that obesity is also an important predictor of the risk of developing T2DM (Varghese, Cherian; Riley, Leanne and Harvey, 2016). Data from 7000 men who took part in the longitudinal British Regional Heart Study showed that increases in body mass index (BMI), waist-hip ratio (WHR), weight change and the length of time that an individual is overweight were all individual predictors of developing T2DM (Ferrannini & Camastra, 1998).

One of the most common metabolic complications associated with obesity is insulin resistance which reduces glucose uptake, impacts on cellular functioning, and mediates insulin insensitivity in hippocampal neurons. This has been proposed as a potential mechanism for obesity related decrements in cognition, as a function of hippocampal neurons being less able to utilise glucose (Biessels, Bravenboer, & Gispen, 2004; Convit, Wolf, Tarshish, & de Leon, 2003; Hoyer, 2003). Research suggests that obesity related insulin resistance is a key factor in the resulting disruption to neural transmission in the hippocampus, leading to memory and learning impairment (Jurdak & Kanarek, 2011; Lamport, et al., 2009; Lamport, Lawton, Mansfield, Moulin, & Dye, 2014). Structural differences linked to memory processes, such as reduced volume of the hippocampus, have been observed in obese adolescents who co-present with T2DM (Bruehl, Sweat, Tirsi, Shah, & Convit, 2011). Whilst there are no studies to date which have specifically investigated the effects of an acute glucose dose on the cognitive performance of obese individuals, the relationships between BMI, glucoregulatory control and insulin resistance are clear. Further research should aim to elucidate these effects in obese individuals prior to a diagnosis of T2DM.

High-glycaemic index carbohydrate food choices, such as refined sugars, refined cereals, potatoes, and white rice, can have a significant impact on general health and can negatively contribute to obesity and T2DM. Chronic stimulation of pancreatic β-cells by high-glycaemic foods is a key factor in the development of insulin resistance (see section 1.2.1). There is also a multiplicity of evidence from the nutritional neuroscience and neurology literature, which confirms that brain structure and

functionality can be modulated by chronic nutritional manipulations (Lieberman et al., 2005). One of the early indications that obesity is having a negative impact, is the development of oxidative stress which is known to contribute to the development of insulin resistance, as a function of the consumption of an energy-dense diet (Jurdak & Kanarek, 2011).

Of particular interest to this thesis are the relationships between abdominal obesity, the increasing prevalence of T2DM and the increased risk factors of mild cognitive impairments which can be seen in obese populations (for a review see O'Brien et al., 2017), irrespective of age (Elias et al., 2005). There are multiple mechanisms which may be driving these cognitive decrements. One mechanism which may be in play here is decreased hippocampal function brought about by insulin resistance as a function of obesity driven metabolic syndrome.

1.3.4 Physical Inactivity

A sedentary lifestyle is associated with an increased risk of developing T2DM, and even short-term inactivity has been seen to impact on insulin resistance. A study of healthy adults followed a regime of five days of 'bed rest', with a strictly adhered to allowance of 30 minutes out of bed in each 24-hour day (Hamburg et al., 2007). Participant's diet was monitored by a nutritionist and based on foodstuffs that they usually consumed. It was found that participants had a 67% increase in net insulin response, and a 6% increase in their net glucose response (Hamburg et al., 2007). Whilst the health benefits of being physically active are widely known, there is a paucity of research which explains the deleterious effects of physical inactivity, with many of the studies reporting the effects on individuals who are at 'bed rest' or completely immobilised. A recent study which argued that a realistic approach needs to be in the context of diminishing physical activity rather than complete immobilisation, utilised a more gradual decrease in activity and evaluated the effects of daily 'step reduction'. The authors found that even short-term physical inactivity led to an increase in peripheral insulin resistance (Bowden Davies et al., 2019).

Increasing daily physical activity, which is considered to be a useful intervention for T2DM or prediabetic individuals, is known to have a positive impact on glycaemic management. Even the avoidance of a sedentary lifestyle or engaging in low intensity activity has been found to have a positive impact on insulin resistance and the maintenance of blood glucose homeostasis in this population (for a review see Colberg, 2012). A recent study of individuals with impaired glucose tolerance or recent diagnoses of T2DM, investigated the relationship between daily exercise habits

and measures of glucose tolerance, insulin sensitivity and β cell response (Temple et al., 2019). Study outcomes found that although the mechanism remains unclear, that higher levels of activity were associated with higher levels of insulin sensitivity, but not with measures of glucose tolerance or β cell response. A recent evaluation of the data of 957 participants with prediabetes from the Whitehall II longitudinal study (Batty et al., 2007), found that physical activity has also been seen to attenuate hyperglycaemia in prediabetic females who were aged over 50 years (Færch et al., 2017). Conversely, a review of studies which explored the effects of physical activity on individuals with impaired glucose tolerance, found that diabetes risk could not be attributed to activity levels independently of other changes such as diet or weight loss (for a review see; Yates, Khunti, Bull, Gorely, & Davies, 2007).

1.3.5 Smoking

Smoking is a risk factor for insulin resistance and the subsequent development of T2DM. Individuals with T2DM who smoked one cigarette per hour over a period of 6 hours, were seen to have a reduction in their insulin sensitivity as a result of a decrease in peripheral glucose uptake (Attvall et al., 1993). An interesting study explored the diabetes related risk of smoking in 1300 (654 males) Caucasian non-diabetic individuals who were first-degree relatives of T2DM individuals (Piatti et al., 2014). An OGTT was conducted to assess glucose tolerance, this revealed that smokers' glucose tolerance was significantly impaired relative to non-smokers. Further study outcomes demonstrated that smoking was strongly associated with impairments in glucose metabolism, insulin sensitivity, and insulin secretion.

This negative impact on glucose tolerance has also been reported in smokers without this familial disposition to T2DM. A study of 152 physically active, adult male smokers, who were epidemiologically similar, found that 66% had abnormal glucose metabolism, and decreases in glucose tolerance was correlated with insulin resistance, and there was a direct association between glucose intolerance and smoking years (Parchwani et al., 2013). From these results the authors concluded that insulin resistance is induced by smoking cigarettes.

1.4 Impact of Poor Glucoregulation

1.4.1 Cardiovascular Outcomes

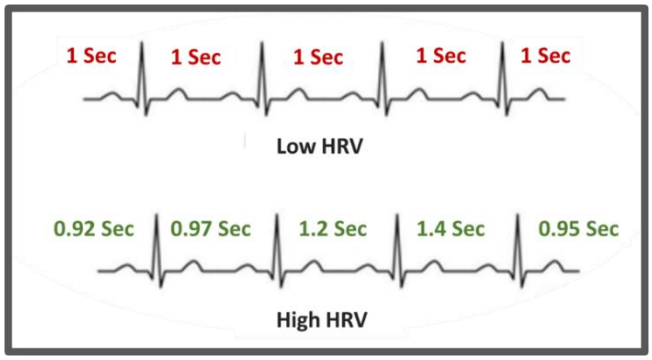
1.4.1.1 Implications in Type 2 Diabetes

Poor glucoregulatory control is associated with changes in heart rate variability and cardiovascular autonomic diabetic neuropathy (CAN). Individuals who have elevated risk for developing T2DM, were seen to have impaired HRV (Penčić-Popović et al., 2014). For a detailed description of HRV see section 1.4.1.1.1 below. It is also known that a relationship exists between high levels of consumption of sugary foods, and cardiovascular risk factors such as impaired glucose metabolism, T2DM, obesity, hypertension and increases in blood lipids such as triglycerides, cholesterol and fat phospholipids in the blood (Jern, 1991; Kopp, 2005; Spellman, 2009).

1.4.1.1.1 Heart Rate Variability

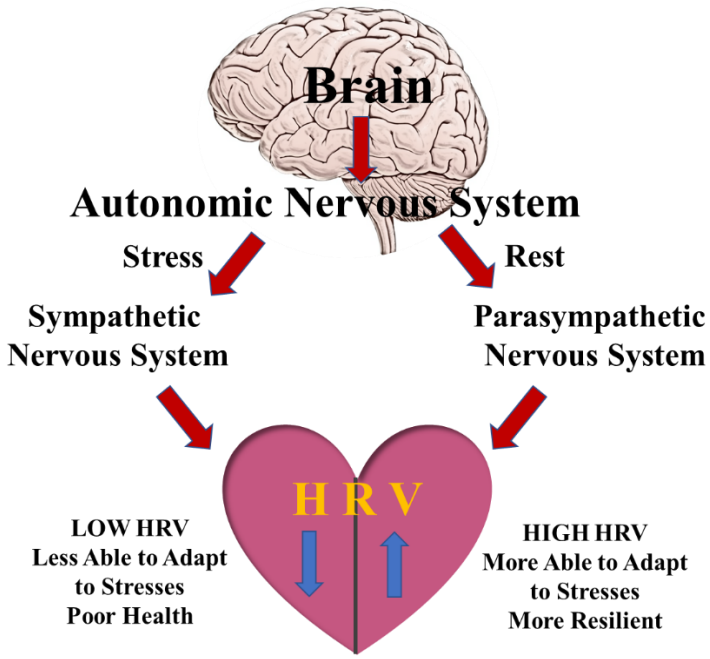
Heart rate variability is controlled by the autonomic nervous system (ANS) which is subdivided into the sympathetic nervous system (SNS), and the parasympathetic nervous system (PSNS). In the cardiovascular system the SNS and the PSNS function antagonistically to maintain a state of balance between vital functions. These two systems are not opposites, but complex interactions occur between the two whereby each system can inhibit the other presynaptically. Heart rate variability is defined by the temporal variation between consecutive heart beats, known as R-R intervals. This nonstationary balance drives heart rate variability by fluctuating the R-R intervals of consecutive heart beats (Xhyheri et al., 2012). The concept of a ‘nice regular heartbeat’ is a misleading myth and indeed, is not desirable because variability in heart rate demonstrates the ability to adapt to stresses in the environment. Low levels of heart rate variability appears more like a steady, metronome-like heartbeat and is associated with poor health and demonstrates an inability to adapt to these stresses, whereas high HRV, or more variable heart rate, is indicative of the individual being more readily able to react to stresses and take action (for a meta-analysis see Kim et al., 2018; Shaffer et al., 2014), see Figure 1.2 below.

Figure 1.2 Schematic representation of the variability in R-R intervals



Impairment of HRV is known to reflect dysfunction in the ANS and is also associated with the development of metabolic syndrome and coronary heart disease (Aso et al., 2006), see Figure 1.3 below.

Figure 1.3 Schematic of the autonomic nervous system and the impacts of heart rate variability.



A further complication of T2DM is cardiovascular autonomic neuropathy (CAN). A serious complication of diabetes, CAN causes damage to the nerve fibres of the autonomic nervous system that stimulate the heart and blood vessels. As a result, abnormalities in heart rate control and vascular dynamics occur (Vinik & Ziegler, 2007). A frequently undiagnosed comorbidity of T2DM and, in individuals with type 1 diabetes, there is an association between CAN and increased mortality

rates (Rosengård-Bärlund et al., 2009). The gold standard measure of CAN is HRV which can be seen to be decreased in individuals with T2DM (For a meta-analysis see Benichou, et al., 2018). Benichou et al. argue that alterations in glucose metabolism attenuates both the sympathetic and parasympathetic HRV activity which then results in cardiovascular autonomic neuropathy. In T2DM patients low HRV is also considered to be a risk factor of sudden cardiac death (Balkau et al., 1999; Kataoka et al., 2004) and in a diabetic population low HRV was associated with excess mortality (Zentai et al., 2008). In young T2DM diabetic adults a more acute cardiovascular risk profile and low HRV was observed (Shah et al., 2020) and subjects were found to have lower root mean square of successive differences between normal heartbeats (RMSSD) and pNN50 which are indicative of parasympathetic loss. The pNN50 is a technique first conceived by Ewing, Neilson and Travis (1984) for assessing parasympathetic activity which evaluates the mean number of times that RR intervals were greater than 50 ms. Ewing et al. observed that over a 24-hour period, diabetics with parasympathetic damage had significantly lower incidences of RR intervals which were greater than 50 ms compared to healthy subjects.

Research investigating HRV in young people, with and without type 1 diabetes, observed early indications of CAN with low HRV in the diabetic subjects which the authors argued was driven by hyperglycaemia (Jaiswal et al., 2013). Investigating the effects of glycaemic control in T2DM individuals, without a diagnosis of CAN, it was found that using an insulin regime to optimize glycaemic control found improved sympathetic and parasympathetic activity, the authors suggest that an insulin intervention could be utilised to reverse CAN in T2DM patients (Mba et al., 2019). A further study investigating the relationship between HRV and a modestly increased risk of the development of T2DM in healthy non-diabetic individuals (mean age 50 ± 14.4 years) used the Finnish Diabetes Risk Score (FINDRISC) to split participants into two groups (Penčić-Popović et al., 2014). The authors concluded that subjects who were observed to have increased risk of T2DM were also seen to have impaired heart rate variability, specifically those with higher risk scores were seen to have lower values for parasympathetic modulation (RMSSD, pNN50 and High Frequency (HF)) and sympathetic modulation (Low Frequency (LF)).

1.4.2 Cognitive Impact of Poor Glucoregulation

Evidence from across a wide range of diseases and disorders highlights the important role of glucose regulation in maintaining cognitive functioning. Disorders associated with declining glucoregulatory control often present with concurrent cognitive decline and impaired glucose tolerance, which has

been seen to impact cognition negatively (for a review see Lamport et al., 2009). Insulin resistance and obesity are both risk factors for memory impairment, and Cheke et al., (2017) also found an association between these conditions and reductions in functional activity across the core brain areas which support episodic memory. Decline in glucoregulatory control is reported to be a function of normal aging (Messier, Tsiakas, Gagnon, Desrochers, & Awad, 2003) and is also a key risk factor for the onset of dementia (Cholerton, Baker, & Craft, 2013). Poor glucoregulatory control is also implicated in a range of disorders presenting with cognitive impairments, such as obesity (Craft & Watson, 2004), mild cognitive impairment (Messier, 2004; Messier, et al., 2003; Riby, et al., 2009), Alzheimer's Disease (Messier, 2003), Type 1 diabetes (for a review see Li et al., 2017), and Type 2 diabetes (for a review see Barbagallo, 2014). Many of the factors contributing to these disorders are overlapping however, poor glucoregulation and comorbid memory decline appear to be common to each of the following conditions.

1.4.2.1 Normal Aging

Whilst the existence of age-related decrements in episodic memory is accepted, it remains unclear what the nature of these changes are. It is generally accepted that recognition memory is seen to have declined in older adults in comparison to younger adults, however, other factors may mean that this is not a simplistic concept. One meta-analysis, which did acknowledge age-related decrements, revealed differences in how younger and older adults made judgements about previously seen or novel items (Fraundorf et al., 2019). The meta-analysis found that older adults, compared to younger adults, demonstrated a reduced ability to discriminate between previously seen and novel items in recognition tasks, particularly for novel items which were deemed as semantically related to the targets. The authors suggest that this demonstrates that older adults are more reliant on semantic information and that age-related differences in decision making may also have an impact.

Age-related decrements found in older individuals are often seen to target episodic memory, and there is some evidence that this decline is related to impaired glucose tolerance which is increased in older adults (Messier, et al., 2003). Messier et al. also suggest that cognitive impairment may be present prior to glucoregulatory control reaching a T2DM diagnostic level. One study found that, non-diabetic older females had both higher fasting glucose levels and 2 hour OGTT, which were both correlated with impaired performance on episodic and semantic memory tasks (Rolandsson et al., 2008).

The precise neural mechanisms which are underpinning cognitive aging are as yet unclear, although reduced volumes in brain structures such as the caudate nucleus of the basal ganglia, prefrontal cortex, cerebellum, and the hippocampus are commensurate with a normal ageing process. A longitudinal MRI study found that increased atrophy in the hippocampus was significantly associated with age at the rate of 0.04 ± 0.02% per year in a cohort of cognitively normal older adults (age range: 58 to 87 years) (Du et al., 2006). The reduction in volume of these structures, which consequentially results in a decrease in the number of synapses and white matter integrity, all potentially lead to age-related cognitive deficits (for a review see Depp, Harmell, & Vahia, 2012).

A further mechanistic pathway to cognitive decline in normal aging is the presence of tauopathy (for a review see Saha & Sen, 2019). Pathological effects of tau protein are not limited to Alzheimer's disease but can also be a contributing factor in various neurodegenerative conditions, including normal ageing (Crary et al., 2014). A possible explanation for tauopathy may be that age-related impairment of the proteasome degradation mechanism, which removes unwanted tau protein, results in a pathological tau accumulation (Fischer et al., 2009).

1.4.2.2 Obesity

In 2018 in the UK, 67% of men and 60% of women were classed as overweight or obese (Official statistics, 2020) with these figures including 26% of men and 29% of women categorised as obese. There is growing evidence of an association between obesity and cognitive impairment in almost all domains of cognition (for reviews see Pedditizi, Peters, & Beckett, 2016; Prickett, Brennan, & Stolwyk, 2015) and improvements in memory and attention have been reported following weight loss (for a systematic review and meta-analysis see Veronese, et al., 2017). Of particular concern is the link between obesity related insulin resistance and both cognitive decline, and neurodegenerative disorders (Craft & Watson, 2004). Obesity is a contributing factor of metabolic syndrome, which is the clinical term for a combination of common conditions such as insulin resistance, high blood pressure (hypertension) and obesity. It is estimated that 1 in 3 adults over 50 years of age in the UK are affected. Whilst global figures for metabolic syndrome are unavailable, based on a prevalence of approximately three times that of diabetes, over one billion individuals worldwide are likely affected (Saklayen, 2018). Whilst it has been well established that the risk of developing insulin resistance is increased by obesity (Bonadonna et al., 1990; Matsuzawa et al., 2011), it has only been recognised quite recently that insulin and insulin resistance play a role in the health of the brain and cognition. Specifically pertinent to this thesis, both obesity and insulin

resistance have been seen to impact on episodic memory performance with reduced brain activity seen in the core recollection network (Cheke et al., 2017). An imaging study exploring the effects of weight reduction in overweight post-menopausal females, found significantly improved episodic memory of faces and increased anterior hippocampal activity during episodic memory encoding (Boraxbekk et al., 2015).

Animal studies involving induced obesity, by feeding of a high-fat diet, have indicated modifications in the structure and functionality of the hippocampus, alongside decrements in memory and learning (O'Brien et al., 2017). One mechanism which may explain this is that this hippocampal damage may be due to an increase in permeability of the blood-brain barrier, allowing entry of free fatty acids, cytokines, and triglycerides. O'Brien et al. suggest that this potential mechanism provides a link between the breakdown of the blood-brain barrier and the cognitive impairment which can accompany obesity. An episodic memory study of young, heathy adults (mean age 24.62 years; mean BMI 25.7, range 18-51.7), of whom 24 were overweight or obese, found that there was a significant relationship between episodic memory task performance and higher BMI (Cheke et al., 2016).

In a study which explored sustained attention in a cohort of young adults of a healthy weight (BMI = 18.5 – 24.9) and obese individuals (BMI = >30), measures of BMI found that higher fasting glucose was associated with poorer performance in a Go/No Go conflict task, particularly in those individuals who had prediabetic levels of glucose tolerance (see section 1.2.3) (Hawkins et al., 2016). Individuals who had a high BMI, but otherwise had normal levels of glucoregulatory control, performed comparatively to individuals with a healthy BMI.

Hippocampal damage may be involved in a negative cycle which helps to progress obesity. In addition to playing a role in episodic memory, which facilitates memory of what an individual has consumed, the hippocampus is also involved in how we respond to hunger and satiety cues (Beilharz et al., 2015). Taken together, these effects of hippocampal damage may be the foundation and the consequence of excessive calorific consumption and obesity.

1.4.2.3 Mild Cognitive Impairment

Mild cognitive impairment (MCI) can be defined as an intermediary state which falls between normal cognitive aging and the symptoms of dementia, specifically those symptoms seen in Alzheimer's Disease (AD) (for a review see Petersen & Negash, 2008). The estimated rate at which MCI affected individuals undergo conversion from mild cognitive impairment to dementia is 9.6% (for a meta-

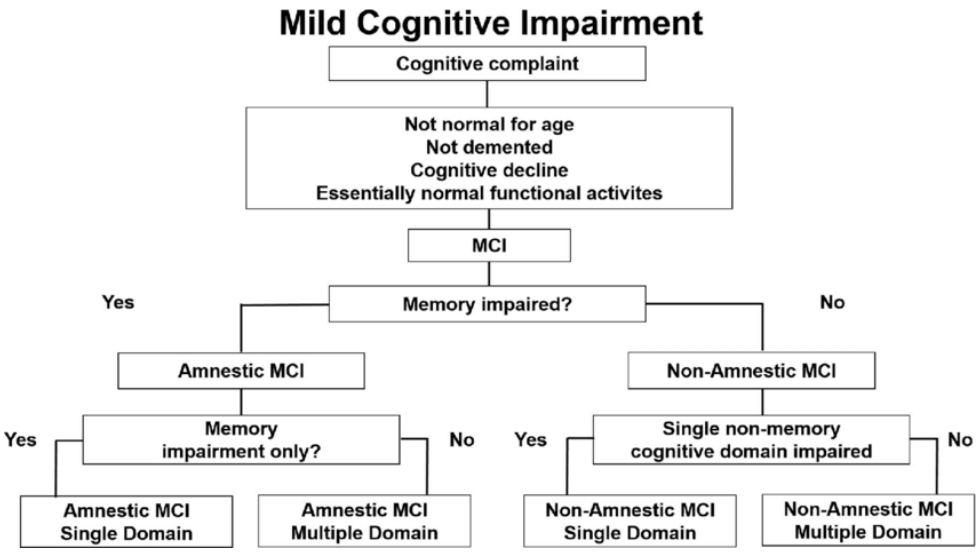
analysis see Mitchell & Shiri-Feshki, 2009). Early recognition of MCI gives opportunities for interventions which can slow the degenerative process. Previously, diagnosis of MCI was based on five criteria (see Table 1.2), that the individual needed to meet (Petersen et al., 1999).

Table 1.2 Diagnostic criteria for mild cognitive impairment used prior to 2003.

1. Memory complaint, preferably qualified by an informant
2. Memory impairment for age
3. Preserved general cognitive function
4. Intact activities of daily living
5. Not demented

Initially, it was believed that all cases of MCI were high risk for dementia or AD, and the focus of the criteria was on memory loss. However, it was observed that not all cases of MCI involved memory loss, and in 2003 a further diagnostic algorithm was created which included two subtypes (see Figure 1.4. below). The MCI subtypes are dependent on whether memory loss is present or not, and these subtypes are defined as a-MCI 'amnesic' (including memory impairment) and MCI 'non-amnesic' (non-memory cognitive domains impaired) (Petersen & Negash, 2008).

Figure 1.4 Current diagnostic algorithm for diagnosing and subtyping MCI (adapted from Petersen R, Negash S. (2008), *CNS Spectrum*. Vol 13, No 1



It has been commonly reported that there is an association between MCI and decrements in levels of glucoregulatory control (Messier, 2004; Messier, et al., 2003; Riby, et al., 2009). It appears that the episodic memory decrements seen in MCI, follow the same mechanistic pathways as other pathologies where memory deficits are present as a function of poor glucoregulatory control. Improvements in MCI have been seen following interventions which reduce body weight, improve insulin tolerance, and improve levels of fasting blood glucose (for a review see Pappas et al., 2019). One such 3 year progressive study which explored the effects of intermittent fasting, found that MCI affected older adults who followed an intermittent fasting regime, had improved cognitive scores and at a 36 month follow-up assessment had returned to improved cognitive function (Ooi et al., 2020). Multiple interventions to defer cognitive decline in MCI affected individuals have been suggested, including pharmacological and non-pharmacological approaches, which have conferred benefits on cognition, structural benefits as well as improved quality of life and overall well-being (for a review see Lissek & Suchan, 2021). In a study of healthy adults compared to adults with MCI, no effect of group was found in terms of accuracy or response times. However, non-diabetic MCI adults (mean age 73 years, SD 5.4) were seen to have higher baseline levels of fasting blood-glucose compared to non-MCI adults (mean age 71 years, SD 5.6). (Riby et al., 2009). These differential fasting blood glucose levels significantly predicted group membership in the populations tested and provides evidence of compromised glucoregulatory control in older individuals with MCI.

1.4.2.4 Dementia

Dementia is a syndrome which includes progressive neurodegenerative diseases such as Alzheimer's disease, Lewy body disease, frontotemporal dementia and vascular dementia (for an overview see Holmes & Amin, 2020). The global prevalence of dementia is increasing rapidly, particularly expanding in low/middle income countries where 58% of cases can be found. The estimated global prevalence of individuals suffering from dementia was 35.6 million in 2010 and it is anticipated that numbers would double every 10 years to an estimated figure of 115.4 million by 2050 (for a review and meta-analysis see Prince, et al., 2013). Poor glucoregulatory control has been identified as a key risk factor for dementia (Bourdel-marchasson et al., 2010; Cholerton, Baker & Craft, 2013; for a meta-analysis see Gudala et al., 2013; Claude Messier, 2003; Ott et al., 1999). The evidence of a relationship between obesity and dementia as a function of an unhealthy diet which is high in sugar and refined carbohydrates, which leads to elevated blood glucose levels and subsequently poor

glucose tolerance. This suggests that one plausible mechanism for the development of dementia is hippocampal insulin resistance) (for a review see Biessels & Reagan, 2015), which in turn dis-regulates the removal of blood glucose from the hippocampus by GLUT-4 glucose transporters (see section 1.2.2 for a detailed discussion on cerebral glucose homeostasis.

1.4.2.5 Alzheimer's Disease

Alzheimer's disease, the most common form of the dementia syndrome, is a degenerative disorder which accounts for approximately 60-80% of dementia cases (Alzheimer's Association, 2020). Alzheimer's disease is partly characterised by the build-up of amyloid beta plaques outside of neurons, formed from fragments of amyloid beta protein, the accumulation of these plaques contributes to damage and subsequent neuronal death. The preclinical progression of amyloid beta deposition is very slow and may last for more than two decades before the clinical symptoms of dementia are apparent (Villemagne et al., 2013). A further diagnostic of AD is the existence of tau tangles inside neurons, comprising of tau protein and blocking transportation of nutrients from entering the neurons. Whilst both of these two characteristics subsequently cause damage to neurons and surrounding tissue, which in turn results in atrophy, the sequence is still unclear (Hanseeuw et al., 2019; Sato et al., 2018). Animal research has promoted a theory which suggests that impaired glucose tolerance is associated with increases in amyloid beta protein deposits, potentially causing cognitive impairment (for a review see Messier & Teutenberg, 2005). Messier and Teutenberg suggest that reduced insulin sensitivity in the brain may compromise the clearance of amyloid beta protein. Moreover, a P.E.T study exploring the interaction between glucose metabolism and insulin resistance across frontal, parietal, and temporal lobes found elevated amyloid beta protein deposits in brain regions involved in AD, adding to the body of research that suggests that amyloid beta deposition may be a function of insulin resistance (Willette et al., 2015). One attractive theory suggests that reduced insulin sensitivity reduces the clearance of amyloid beta, consequentially this chronic build-up of amyloid beta causes further insulin resistance which may mediate impaired cerebral glucose metabolism (Hoyer, 2004), with compromised cognitive processes being challenged by the brain's diminishing ability to metabolize glucose as fuel (see section 1.2 for a more detailed description). Medial temporal lobe structures, such as the hippocampus and the entorhinal cortex are heavily involved in the processing of episodic memory. These structures are highly susceptible to the neurodegenerative effects of AD and the resultant deficits in episodic memory are a hallmark feature of AD (Gallagher & Koh, 2011).

1.4.2.6 Type 1 Diabetes

Type 1 diabetes mellitus is most often diagnosed in individuals at a very young age and the major characteristic of the disease is insulin deficiency. Type 1 diabetes is an autoimmune disease in which the immune system attacks the insulin producing beta cells in the pancreas, resulting in the prevention of insulin synthesis. Despite the availability of exogenous insulin, Type 1 diabetes individuals are still not able to regulate their glucose metabolism as efficiently as a healthy individual. However, because the physiological effects of Type 1 diabetes are fluid, it is difficult to achieve constant levels of glycaemic control via insulin therapy. The most common complication of insulin therapy is hypoglycaemia (for a review see Li, et al., 2017), and research exploring its effects on cognition report deleterious effects on memory (Ebadi et al., 2018; Sommerfield et al., 2003). A crossover study, which utilised glycaemic clamps at two randomised visits, assessed cognitive functioning during conditions of both hypoglycaemia, and euglycaemia and it was found that working memory was significantly impaired during hypoglycaemia in individuals with type 1 diabetes (Gejl et al., 2017). These outcomes provide clear evidence of the detrimental effects on cognition, caused by the cumulative effects of poor glucoregulatory control and subsequent hypoglycaemic episodes. Research suggests that recurrent hypoglycaemic episodes increases inflammation and oxidative stress, which in turn leads to hippocampal damage and an acceleration of cognitive decline (for a review see McCrimmon, 2021).

Adults with type 1 diabetes mellitus have been shown to have impaired sustained attention (Van Dijk et al., 2014), and impaired cognitive self-control being seen in patients with schizophrenia (Leung et al., 2014). Both of these populations have challenged glucoregulation.

1.4.2.7 Type 2 Diabetes

The prevalence of T2DM is alarming, globally there were 171 million afflicted individuals in 2000 and the expectation is that this will rise to 366 million by the year 2037 (Wild et al., 2004). Increased obesity and greater life expectation are a critical factor in the proliferation of this pervasive disease. Generally, T2DM can be managed by careful control of the individual's diet and in these instances, type 2 diabetics are classed as 'non-insulin dependent diabetes mellitus' (NIDDM).

Persistent chronic disruption of glucoregulation, such as that seen in poorly controlled T2DM results in impaired insulin sensitivity, when insulin receptors no longer respond to insulin, leading to elevated blood glucose levels. Impaired glucoregulatory control can increase the risk associated with

the development of cognitive deficits (Allen et al., 2004; for a review see Wong et al., 2014). There is a substantial amount of evidence in the literature which suggests that individuals with T2DM are potentially at risk of cognitive impairment in domains related to episodic memory, and subsequently dementia (for a meta-analysis see Sadanand et al., 2016; Schweizer & Dalgleish, 2016). In a study of 1288 older individuals with T2DM, a relationship between waist circumference and overall cognitive functioning was observed, with increased central adiposity being correlated with lower cognitive performance in women (West et al., 2016). T2DM can potentially lead to lasting cognitive decrements such as reduced functional activity in brain areas, such as the hippocampus, angular gyrus, and dorsolateral prefrontal cortex, all of which support the encoding and retrieval of episodic memory (Cheke et al., 2017).

There is increasing evidence from the neuroimaging literature of T2DM related neurocognitive alterations to brain structure and functionality. A review exploring the neural correlates of T2DM identified studies which found changes such as global brain atrophy and enlarged ventricles (for a review see Lee et al., 2014). This review reported some studies indicating that impaired glycaemic control may impact on the advancement of cerebral atrophy. Whilst there is a paucity of research that encompasses electroencephalogram recording in the context of T2DM and episodic memory, there is an interesting functional magnetic resonance imaging (fMRI) study of 22 twin-pairs of older adults who were discordant for T2DM (Parsons & Gold, 1992). Findings from this study showed that during encoding of episodic memory, there was evidence of dysfunction in neuronal network activity for the T2DM participants in comparison to the non-diabetic controls. The authors highlight that the shared genetics, age, sex, and shared environment in early life support the robustness of their findings, that T2DM is underpinning the dysfunction. Evidence from studies such as these provide further evidence of the negative impact of disrupted glucoregulatory control on cognition, and specifically episodic memory.

Section Summary

Evidence from the above sections gives a clear indication of the cognitive damage which can result from poor glucoregulatory control. Individuals in all the above categories have poorly regulated glucose to a varying degree, and in all of these cases it is apparent that poorly controlled levels of blood glucose can lead to cognitive problems in these populations. However, it is necessary to consider that some of the above categories do not exist in isolation, and very often individuals will be

afflicted with more than one condition; for example, whilst T2DM individuals, and indeed Type 1 diabetes individuals have poor glucoregulatory control, they quite often have other conditions which impact on cognition. The comorbid presence of obesity, advanced-age, or other co-presenting conditions of diabetes or metabolic syndrome, such as cardiovascular disease, can be considered as a confound to establishing the real cause of any cognitive decrements.

Having considered the consequences of poor glucoregulatory control, the next section will explore the cognitive impact of temporarily elevating circulatory blood glucose levels by administering an acute glucose dose.

1.5 The Effects of Glucose Administration

The potential of glucose to facilitate cognitive performance was first proposed in the 1950s when Hafemann (1955) explored the relationship between fatigue and the blood glucose levels of schoolchildren. The author found that the children's cognitive performance and levels of concentration were improved following an acute glucose dose. Since this time there has been a broad body of research which investigated whether acute glucose administration has the capacity to facilitate cognitive performance or attenuate impairments in cognitive functioning. These investigations include multiple populations, both healthy and compromised, and across the lifespan.

Acute glucose ingestion has been shown to facilitate cognitive performance on selected tasks and this effect is now well accepted as a robust phenomenon (for reviews see Messier, 2004; Riby, Perfect, & Stollery, 2004; Smith, Riby, Eekelen, & Foster, 2011). However, these effects, which are particularly reported for tasks targeting episodic memory and attention/psychomotor performance domains, are somewhat inconsistent across the literature, even within studies utilising similar methodologies..

Previous research has established that a 25g glucose dose is the optimum effective glucose dose to invoke cognitive facilitation (Boyle et al., 2018; Parsons & Gold, 1992; Sünram-Lea et al., 2011). This premise was validated across the lifespan by a study exploring glucose facilitation of memory retrieval in both young and older populations (Riby et al., 2006). However, the authors suggest that, as glucose regulation is seen to decline with age these older adults may have needed a higher dose in order to benefit from the enhancement effect of glucose. One limitation of this study was that measures of participants glucoregulatory control were not assessed.

1.5.1 Cardiovascular Impact of Glucose Administration

There is a paucity of research investigating the impact of glucose administration on cardiovascular measures such as heat rate variability, which serves as a measure of cardiovascular autonomic function (see section 1.4.1.1.1). Foods high in sugar are associated with risk factors, such as obesity and impairments in glucose tolerance, for cardiovascular disease (Kopp, 2005; Spellman & Craig W, 2009). A recent study investigating the cardio-autonomic stress response following carbohydrate ingestion (a dose of 1 g/kg of body weight) in a population of healthy adults aged 18 – 65 years (BMI of 18.0–29.9, and normal overnight fasting blood glucose levels (Eckstein et al., 2022). The authors found that following a dose of 1 g/kg of body weight of carbohydrate (glucose, fructose, or a combination of the two) found that even small alterations in blood glucose prompted a cardio-autonomic response. In terms of heart rate variability measures, SDNN, RMSSD and pNN50 were lower following the carbohydrate drinks compared to the placebo drink. Furthermore, this study found declines in HRV as levels of blood glucose increased.

1.5.2 Cognitive Impact of Glucose Administration

A recent systematic review and meta-analysis reviewed the effects of ingested glucose on cognition, with within-subjects design being used for 18 studies and a between-groups design utilised for a further 17 studies (Reche, 2020). The most prevalent cognitive tasks included in the meta-analysis calculation were immediate and delayed recall, a digit span memory task. Seven of the studies had focused on immediate recall, and overall meta-analysis of both between-groups and within-groups studies revealed that cognitive performance was significantly increased following administration of an acute glucose dose ($p=0.02$). However, when separate meta-analyses were conducted for the between-groups and the within-groups studies, this significant effect was only present for immediate recall tasks in the between-groups studies ($p=0.003$) with the within-groups effect being non-significant ($p=0.34$). Reche suggests that glucose may be benefitting cognition to a small degree, specifically for recognition memory and attentional studies. However, as within-groups designs are generally considered to be more robust because participants are being assessed against their own placebo control condition, the data from between-groups designs may be giving a false picture of the effects of glucose and may be a limitation of the meta-analysis.

Additionally, it is widely suggested that glucose facilitation commonly occurs for tasks which evoke high cognitive demand and evidence from the literature shows differential outcomes for younger versus older adults. Evidence from behavioural studies suggest that glucose enhancement of episodic

memory in healthy young adults is modulated by task effort (demand) rather than hippocampal mediation of glucose, with some studies suggesting that glucose facilitation is only seen in healthy young adults when tasks necessitate a high intensity of cognitive demand (see section **Error! Reference source not found.** below for more detail on this concept) (Brandt, Gibson, & Rackie, 2013; Fairclough & Houston, 2004; Kennedy & Scholey, 2000; Riby, 2004; Scholey et al., 2013; Scholey, Harper, & Kennedy, 2001; Scholey, Laing, & Kennedy, 2006b; Sünram-Lea, Foster, Durlach, & Perez, 2002).

1.5.2.1 Executive Function

Is identified as the management, or regulation of cognitive processes such as problem solving, working memory, control, flexibility and planning and execution of tasks. An acute glucose dose has been seen to enhance executive functions involving self-control and inhibition such as the Stroop Task (Owens et al., 1997; Stroop, 1935). In a study of young adults, following a 25 g dose of glucose there was a trend, although non-significant, towards enhanced performance for the Stroop colour-naming task in which the most demanding of tasks were seen to show the most sensitivity to ingested glucose (L. A. Brown & Riby, 2013a). However, another study (Owen et al., 2012) did not find any enhancement effects of correct responses or RTs for the Stroop task following either a 25 g or a 60 g glucose dose. Exploring the effects of a 50 g glucose load in a population of older adults (mean age 67.7) on a series of executive tasks requiring attentional resources, which involve switching and divided attention, such as the Stroop and computerised dual-tasking; glucose was seen to have a short-term facilitative effect following an overnight fast (Gagnon et al., 2010).

1.5.2.2 Working Memory

The concept of working memory is the temporary storage of information which is then manipulated to perform complex cognitive tasks. In a dose-response study glucose was seen to facilitate a special working memory task following a 25 g glucose dose but no effects were seen after administration of a 15 g, 50 g or 60 g dose. A multi-dose study found enhanced performance following a 25 g glucose dose after a 2 hour fast for the Serial 7's task, a demanding working memory task and additionally that a 60 g dose following an overnight fast Conversely, at 60 minutes post-ingestion, impairments in the quality of working memory were seen in healthy young adults following a 25 g glucose dose compared to a placebo drink (Jones et al., 2012b). However, the authors suggest that this may be due to the fast metabolism of glucose and the impairments may be the result of a subsequent drop in blood glucose levels mediated by increased insulin release.

1.5.2.3 Attention and Vigilance

Sustained attention is the capacity to remain attentive during processing of stimuli presented in a repetitive manner. The non-arousing nature of such stimuli leads to habituation which distracts from the distractor arrays (Robertson et al., 1997). The Flanker paradigm and the Sustained Attention to Response Task (SART) (Robertson et al., 1997) are conflict tasks commonly used as a measure of attentional control and sensorimotor processing. SART requires a high degree of continuous attention to make accurate responses while at the same time other cognitive processes, such as memory, are minimised. Robertson et al. suggested that lapses in attention leading to errors may be partly attributed to decrements in sustained attention. Another study (Birnie et al., 2015), again exploring the enhancement effects of glucose ingestion, presented SART at two different speeds. No treatment effects for SART accuracy or RT response speed were reported but a main effect of speed highlighted that participants responded more quickly when the presentation of stimuli was speeded up.

Glucose has been seen to slow flanker response RT (Hope et al., 2013) and reaction speeds to a sustained attention task were slower following a 50 g glucose dose (Adan & Serra-Grabulosa, 2010). Whilst the Hope et al. study did assess blood glucose levels, no measures of glucoregulatory control were taken.

Attentional deficits in sustained attention are associated with damage to the frontal lobe and white matter following traumatic brain injury. Robertson et al. (1997) found that attentional lapses in SART correlated with brain damage severity and self/relative-reported attentional failures. A further study which specifically explored the effects of glucose ingestion and glucoregulatory control on older adults with mild cognitive impairment (MCI) compared to normal older adults (Riby et al., 2009). This study found no effects of either group or glucose for accuracy but for response RTs there was a near significant ($p = 0.06$) effect of group, with faster response times for MCI adults. Whilst Riby et al. did not include glucoregulation as a variable in the SART analysis, they did find that throughout the testing sessions, the MCI group had higher blood-glucose levels. Additionally, baseline levels of blood-glucose significantly predicted group membership in the populations tested by Riby et al.

This thesis will explore the possibility that glucoregulatory control may have an impact on attentional resources and additionally, investigating performance differences between better and poorer regulators following a glucose dose.

1.5.2.4 Psychomotor Speed

Along with walking speed, decrement in psychomotor speed is considered to be associated with increased risk of poor health-related outcomes, such as dementia in elderly adults. A longitudinal study finding that from a cohort of 1265 (mean age: 74 years) at the 12 year follow-up there were 203 cases of dementia (Kuate-Tegueu et al., 2017). Poorer performance on psychomotor tasks such as aiming or line-tracing, choice reaction time, co-ordination tasks has been associated with low blood glucose levels in both non-diabetic and diabetic adults (for a review see Feldman & Barshi, 2007). Effects of glucose administration on psychomotor skills are mixed. A study of younger versus older adults found that a 25 g glucose dose facilitated memory response speed and tracking task accuracy during performance of a secondary task in older but not younger adults (Macpherson et al., 2015). A study of healthy undergraduates (mean age 20.8, SD 1.85) found that a 50 g glucose dose enhanced performance on the choice reaction time task, with faster RTs following glucose compared to placebo (Giles et al., 2012). Conversely, Messier et al. (2011)found that a 50 g glucose dose did not enhance the performance of healthy undergraduates on a digit symbol coding task, suggesting that glucose facilitation in this population is linked to glucoregulatory control.

1.5.2.5 Mood and Energy

The is a paucity of literature which address the impact of glucose administration on mood and energy. An early study found that a 50 g glucose dose following an 8 hour fast elevated vigilance but the authors suggest that this effect was being modulated by the expectation of glucose consumption (Green et al., 2001). However a study exploring the differential effects of macronutrients found no effects of a 25 g glucose dose on the subjective measures of mood and energy in a cohort of young adults (Jones et al., 2012a). The findings of a recent review suggest that, up until publication date, there is no supporting evidence for glucose facilitation of subjective mood (for a review see Boyle et al., 2018)

1.5.2.6 Memory

1.5.2.6.1 Recognition Memory

Episodic recognition memory has two components, recollection, and familiarity. Memories which allow us to not only recall whether we have previously seen an item or an event, but also have enriched contextual details, are categorised as ‘recollection’. On the other hand, a memory which

lacks this episodic richness and can be construed as 'a feeling of knowing', is categorised as 'familiarity'. There is body of research which proposes that recognition memory is potentially targeted by glucose facilitation via the administration of an acute glucose dose (for reviews see Messier, 2004; Riby, Perfect, & Stollery, 2004; Smith, Riby, Eekelen, & Foster, 2011). Findings across the glucose enhancement literature are mixed and the mechanisms supporting this potential facilitation are unclear (see section 1.5 for a more in-depth discussion). Recent fMRI explorations are beginning to unravel the functional roles of regions in the medial temporal lobes (MTL) and a network of cortical regions with connectivity to the MTL has been identified as being consistently activated during successful recollection processes (Rugg & Vilberg, 2013). Previous research had intimated that when the remember/know paradigm was utilised, ERP evidence showed two distinct effects being evoked by episodic recall of 'recollection' and 'familiarity' judgements, supporting the view that these two processes were temporally and topographically different (Rugg et al., 1998).

Structural Involvement

The medial temporal lobe, which is important for episodic and spatial memory processes, includes the hippocampal system, perirhinal system, entorhinal cortex and the parahippocampal cortex. Aggleton and Brown (2006) argue that within the medial temporal lobes there are two functionally different memory systems pertaining to episodic memory; the hippocampal system, associated with the episodic richness of recollective memory, and the perirhinal system, associated with earlier occurring familiarity judgements representing a 'feeling of knowing' but without the memorial support of contextual detail.

There is considerable debate around the role of the hippocampus in memory. The hippocampus is known to be vulnerable to damage by hyperglycaemia (Cervos-Navarro & Diemer, 1991; Mattson et al., 1989; McEwen, 1997) and the basis of the task domain hypothesis is supported by the known effects of impaired glucose tolerance on memory function (see section 1.2.3 for a more detailed account of impaired glucose tolerance). As such, there are multiple dysfunctional mechanisms which may be driving these cognitive decrements. As the hippocampus is rich in insulin receptors, one possible mechanism which may be aligned to the cognitive deficits discussed here is decreased hippocampal functionality, brought about by insulin resistance as a function of poor glucoregulatory control or longer-term neurotoxicity resultant from elevated levels of insulin. The hippocampus is insulin-sensitive (McNay et al., 2010) and associations between impaired insulin signalling, which can be seen in T2DM and Alzheimer's disease, and cognitive impairment have been previously reported

(Bourdel-marchasson et al., 2010; Cholerton, Baker & Craft, 2013; Greenwood & Winnocur, 2005). Insulin is also known to play a major role in regulating synaptic plasticity in the hippocampus where large numbers of insulin receptors are expressed (McNay & Recknagel, 2011; Zhao et al., 2004).

A further explanation may be that this dysfunction occurs because of failure to maintain glucose homeostasis following activity generated depletions of hippocampal interstitial glucose concentrations (W. Chen et al., 1993; Lamport et al., 2009; Mcnay et al., 1999; McNay et al., 2006; McNay & Sherwin, 2004). Furthermore, decreased hippocampal volume but not overall brain atrophy is observed in impaired glucose tolerance (IGT) and T2DM. Convit (2005) suggests that this may arise from chronic hippocampal hypoglycaemia. In consideration of potential memory enhancement, poorer regulators who may have impaired insulin resistance or the inability to restore depletions of interstitial brain glucose in the hippocampus, may benefit from an ingested glucose dose (Convit, 2005; Lamport et al., 2009; Young & Benton, 2014). Conversely, better regulators with efficient maintenance of stable glucoregulatory control would render their cognitive performance less vulnerable.

The neural correlates of recognition memory have also been much debated with some evidence supporting the dual-process model being derived from studies which have investigated patients with hippocampal lesions. Whilst some studies (Aggleton et al., 2005; Holdstock et al., 2002) support a dissociation in the mechanisms of recognition processes, as such, the preservation of familiarity but not recollection following hippocampal damage (Addante, Ranganath, Olichney, & Yonelinas, 2012). There is also a body of literature which refutes this theoretical argument. Manns et al. (2003) found that amnesic patients with hippocampal region damage, exhibited impairment for both 'remembering' and 'knowing' which implicates the hippocampus in both familiarity and recollection components of recognition memory. However, opposing fMRI research posits that remember/know judgement dissociations seen in amnesic patients may not represent dissociations of recollection and familiarity; arguing that whilst the processes of recollection and familiarity may differ, the remember/know paradigm may not investigate them directly (Wais et al., 2006, 2008). Conversely, a recent intracranial electroencephalographic (iEEG) study, monitoring a large number of individuals for epilepsy, also observed that both recollection and familiarity generated high frequency neural activity (HFA) in the hippocampus, as such, suggesting that the hippocampus is directly involved in both of these facets of recognition memory (Merkow et al., 2015).

Evidence for the involvement of the hippocampus comes from lesion studies which have shown that hippocampal damage can cause anterograde amnesia, implicating the hippocampus as being involved in memory encoding. Without the hippocampus new semantic but not episodic memories can be formed. Traditionally, there is a conjecture that the hippocampus does not have an essential role in implicit memory functions, which are without episodic richness or contextual binding. However, there is now an increasing body of research which argues that the hippocampus is involved in implicit memory. Evidence for this was found in a recent lesion study of MCI patients who had MTL damage which was limited to the hippocampus (Addante, 2015). Subjects underwent recognition tasks during EEG recording, and evidence from analysis of the FN400 ERP component suggested that both implicit and explicit memory systems may be reliant on the same underlying brain structures but functioning in physiologically different ways. Conversely, further research (Brandt et al., 2016), found that familiarity was impaired as a result of damage to the entorhinal cortex impaired familiarity, with recollection remaining intact. The authors suggest that the entorhinal cortex supports a process of a long-term familiarity component of recognition memory.

There are two theories of recognition memory which are pertinent to the work in this thesis, namely the dual-process model and the single-process model. There is still much debate in the literature concerning the validity of these models. The single-process model assumes that familiarity (knowing) merely reflects weaker recollection (remembering) and argues that these two processes of recognition memory only differ quantitatively as a measure of memory strength. Differentially, the dual-process model argues that recollection and familiarity are two distinct components of recognition memory which differ qualitatively (M. W. Brown & Aggleton, 2001). Whilst the majority of recognition memory literature supports the concept of the dual-process model, an alternative single-process interpretation has been proposed which centres on signal-detection theory and challenges the remember/know paradigm (Wixted & Mickes, 2010). Whilst the authors suggest that the remember/know procedure may be used to make distinctions between recollection and familiarity-based recognitions, they argue that in the form that it is mostly used, the paradigm distinguishes between strong and weak recall.

There has been a broad body of recognition studies in the literature which propose various dual-process models, all proposing that recognition memory is supported by two functionally different memory systems. One such model contends that the two components of recognition memory, recollection and familiarity are dissociated by speed of retrieval and the degree of episodic richness of the information (for reviews see Rugg & Yonelinas, 2003; Yonelinas, 2002). The dual-process

recognition memory model (Yonelinas, 1994, 2002), argues that recollection supports subjective 'remember' judgements, whereas in the absence of the episodic richness attached to recollection, familiarity supports 'know' judgments which arise from a 'feeling of knowing'. These two processes are believed to operate independently and whilst this concept of separate processes is widely accepted, the role of familiarity remains unclear, and it is still debated whether familiarity is merely a 'weaker' measure of recognition or, whether a separate functional mechanism is in play.

Support for the dual process model can be seen in dissociations in these two distinct processes arising from patient studies. Patients with localised damage to the hippocampal system, which includes the entorhinal cortex, were seen to present with impaired recollection but intact familiarity (Brandt, 2015; Hoppstädter et al., 2015), whereas damage to the perirhinal system was associated with impaired familiarity. However further research (Brandt et al., 2016), found that selective impairment to the entorhinal cortex impaired familiarity whilst recollection remained intact, suggesting that the entorhinal cortex supports a process of a long-term familiarity component of recognition memory.

This dissociation can be explored using Tulving's (1985) Remember/Know paradigm which calls for a subjective declaration from the participant which ascertains whether the recognition is based on the episodic richness of recollection or merely on a feeling of 'knowing' relative to familiarity. To investigate this potential dissociation further, the effects of glucose and glucoregulation on memory are also examined to evaluate the mechanisms supporting these two facets of memory. Sünram-Lea et al., (2008), utilising a remember/ know /guess procedure, found increased correct recollection responses, but not familiarity responses, in healthy young adults (age range 18 – 25 years; mean age 20 years) following glucose administration compared to placebo; offering support for the dual-process model. However other research, exploring the question of whether glucose facilitation was targeting hippocampal memory or whether task demand was a more important determinant of this facilitative effect, employed a secondary hand-movement task during the encoding of verbal stimuli (Scholey, MacPherson, Sünram-Lea, Elliott, Stough, Kennedy, et al., 2013). The authors found that there were no differential effects of glucose for recollection or familiarity responses but suggested that task effort was a more important determinant of glucose facilitation than domain specific hippocampal mediation.

1.5.2.6.1.1 Theories of Glucose Enhancement of Episodic Memory

There is a growing literature supporting the facilitatory effect of elevated blood glucose levels on cognitive functioning (for review articles see Messier, 2004; Smith et al., 2011; Stern and Alberini, 2013; Peters et al., 2020), with episodic memory specifically seeming to be improved. The mechanisms underpinning this effect are as yet unclear, with several competing and valid mechanisms proposed. There are two dominant contending theories which propose to justify the glucose enhancement of recognition memory effect.

The Cognitive Demand Hypothesis

The clearest behavioural evidence for glucose facilitation of episodic memory arises from studies which require an increased level of cognitive effort. The cognitive demand theory proposes that enhancement is related to task demand, whereby the level of task demand moderates the impact of glucose administration, and that this facilitative process is only seen when tasks necessitate a high intensity of cognitive demand (Brandt, Gibson, & Rackie, 2013; Fairclough & Houston, 2004; Kennedy & Scholey, 2000; Riby, 2004; Scholey et al., 2013; Scholey, Harper, & Kennedy, 2001; Scholey, Laing, & Kennedy, 2006b; Sünram-Lea, Foster, Durlach, & Perez, 2002). One suggested mechanism for this effect is that more complex cognitive processing results in greater depletion of circulatory blood glucose levels, which has been observed in a study which did not administer glucose (Scholey, et al., 2006). This effect can also be evoked by the performance of a secondary, effortful task, such as a sequential hand movement task or a mouse tracking tack during the encoding of the stimuli. Donohoe and Benton (1999) suggest that cognitive functioning is susceptible to blood glucose levels, and they propose two potential mechanisms. Firstly, that plasma and cerebral glucose levels are relative, individuals who have greater levels of circulating blood glucose will also have higher levels of cerebral glucose, consequentially more glucose will be available to the brain. Secondly, the authors suggest that potential individual differences in glucoregulatory efficiency will impact on performance, with those individuals with poorer glucoregulation performing less well on certain cognitive tasks. For a résumé of these studies see section 1.5.2.6.1.2.

The Hippocampus Hypothesis

The other dominant theory is that enhancement is related to task domain and relies on the notion that the enhancement effect of glucose is subserved by the hippocampus (Riby, et al., 2009; Riby, et al., 2008; for a review see Riby, 2012; Scholey, et al., 2014; Sünram-Lea, et al., 2008). The hippocampus is known to be vulnerable to damage by hyperglycaemia (Cervos-Navarro & Diemer, 1991; Mattson et al., 1989; McEwen, 1997) and the basis of the task domain hypothesis is supported by the known effects of impaired glucose tolerance on memory function (see section 1.4.2. for examples).

Aggleton & Brown, (2006) suggest that the hippocampus is preferentially involved in 'recollection' based memory, but not 'familiarity'; arguing that familiarity is subserved by the perirhinal cortex. In these terms, the Sünram-Lea et al. (2008) study provides support for glucose enhancement of memory being mediated by the hippocampus and as such, support for the task domain hypothesis. However, these findings may not be robust because as the study used a between-groups design, inter participant variability may have had an impact. Additionally, this study did not find a relationship between glucoregulatory control and memory performance (see section 1.5.2.6.1.1 for a review of these studies).

1.5.2.6.1.2 Glucose Enhancement of Episodic Memory

Since the early 1980's, when glucose enhancement of memory was first highlighted by Lapp (Lapp, 1981), there have been a great many studies which have explored this facilitative effect. Prior to this, it was suggested by (Thorndike, 1933) that improved memory was the result of a reward-related strengthening of association taking place. Messier, Tsiakas, Gagnon, Desrochers, and Awad (2003) argued that this relationship between drinking glucose and pleasure, was not simply producing a cause-and-effect enhancement of memory because the substitution of saccharin found no effects. The next stage of this journey was the discovery that injected glucose had the same effect as when taken orally (Messier & White, 1984). This suggested that the memory enhancement effect of glucose was occurring as a result of a post-ingestion mechanism.

Emanating from the last three decades, is a large body of research from both animal and human studies suggesting that an acute dose of glucose, which subsequently increases circulatory blood glucose levels, has a facilitative effect on cognition. Evidence for this arises from behavioural studies (Boyle, et al., 2018; Reche, 2020; Smith, Riby, Eekelen, & Foster, 2011), and neuroimaging studies (for a review see Peters et al., 2020). Whilst there have been dose response studies which have explored dosages relating to age and body weight, this thesis is concerned with young healthy adults for whom a 25g glucose load has been shown to reliably elevate circulatory blood glucose over the cognitive testing period for this population (Brandt et al., 2006; Hope et al., 2013; Owen et al., 2013; Riby et al., 2011; Scholey et al., 2013).

Young Healthy Adults

There are mixed results in the glucose enhancement literature, with some studies reporting that glucose enhances episodic memory in healthy young adults, whilst other studies failed to find effects of glucose. Evidence from a systematic review suggests that glucose enhancement of memory performance in healthy young adults was more sensitive to an acute glucose dose than were other cognitive domains (Hoyland et al., 2008). Two early studies which compared older and younger adults found that in older, but not younger adults, a 50g dose of glucose significantly enhanced episodic memory (Hall, Gonder-Frederick, Chewning, Silveira, & Gold, 1989; Manning, Parsons, Cotter, & Gold, 1997). Additionally, Hall et al. found that glucose tolerance was a predictor of memory in older but not younger adults. However, this has not been a consistent finding. In young

adults with poorer glucoregulation, a 50g glucose dose, reversed memory impairments that were observed following a saccharin placebo (Messier, Desrochers, & Gagnon, 1999). One limitation of the Hall et al., and Messier et al. studies is that glucoregulatory control was based on samples taken during cognitive testing rather than at rest via an OGTT. Studies to date which have failed to find significant effects of glucose on episodic memory in populations of young adults include; employing a within-groups design and following both 30g and 60g glucose (Azari, 1991); a between-groups design and 50g of glucose (Benton & Owens, 1993); between-groups design and 50g of glucose (Green et al., 2001); using emotional words and a within-groups design (Ford et al., 2002); a between-groups design and following 25g of glucose, tracking performance but not memory was enhanced (Scholey, Sunram-Lea, et al., 2009); between-groups design and following 25g of glucose (Owen et al., 2010); in a between-groups design and after 15g, 50g and 60g doses of glucose (Sünram-Lea, et al., 2011). The mixed results of these studies may be due to methodological differences such as between-groups versus within-groups designs, measures of glucoregulation and differences in the glucose dose. These differences were addressed in Chapters 4 and 5 of this thesis which used a within-groups design, OGTT measures of glucoregulatory control and a standard 25g glucose dose.

In a study of non-diabetic young adults with healthy levels of glucoregulation, Messier et. Al. (2011) found no support for the hypothesis that cognitive performance of poorer regulators would be enhanced following ingested glucose. However, there was a significant relationship between evoked levels of glucoregulation and accuracy for verbal memory tasks, as such positing that administration of a glucose load may specifically target individuals with poorer, but not manifesting as clinical, levels of glucoregulatory control. Messier et al. suggest that their results indicate that cognitive decrements can be seen in those healthy young individuals with poorer, but not yet impaired, glucoregulation.

There are a limited number of behavioural studies involving healthy young adults which found facilitative effects of glucose for episodic memory tasks, and these include a dose-dependent between-groups study of females only, for glucose doses of 300mg/kg and 800mg/kg, however these effects were primacy effects only (Messier, Pierre, Desrochers, & Gravel, 1998). It has also been suggested that glucose enhancement is potentially influenced by initial thirst, with one between-groups study reporting that following a 25g glucose dose (Scholey, Sünram-Lea, et al., 2009). The least thirsty individuals correctly recalled more words following placebo; conversely the thirstiest individuals correctly recalled less words following glucose relative to placebo. The Scholey et al. (2009) study highlighted that participants' hydration state, indicated by self-report measures of

'thirst' may be mediating potential glucose effects. However, it is important to note that the Scholey et al. (2009) study did not include a baseline assessment which may explain the findings. To address this potential, confound, all of the studies in this thesis collected self-report data for physical and mental states, with analyses being conducted to assess potential differential effects.

Neuroimaging Studies

Recent glucose enhancement research has utilised neuroimaging methodologies to explore the facilitative effects of glucose on cognition (for a systematic review see Peters, White, Cleeland, & Scholey, 2020). The eleven neuroimaging studies which met the inclusion criteria for this review included six utilising electroencephalography (EEG), four which employed fMRI and one functional near-infrared spectroscopy (fNIRS) study. Whilst only five studies in the review showed significant glucose facilitation effects, ten studies identified that glucose was modulating the neural corelates of episodic memory and attention, with the one fMRI study not reporting any significant findings. Peters et al. suggest that these neurological effects of glucose on episodic memory and attention, which were often not supported by behavioural evidence, are underpinned by activation of medial temporal and frontal structures. The authors suggest that the lack of behavioural evidence may be due to the small sample sizes of the studies. However, considering the arguments presented in this thesis, it may also be argued that the facilitative effects of glucose may be too nuanced to be detected by traditional behavioural investigations.

Older Adults

Age related studies suggest that glucose enhancement is more evident in older adults (Foster et al., 1998b; for a review see Smith, Riby, et al., 2011). This may be due to the impact of declining glucoregulatory control in older individuals enabling a beneficial effect from ingested glucose. One study of older adults (age range 35-55 years) found that a 25g glucose dose enhanced episodic memory when task demand was elevated (Riby et al., 2008), suggesting that blood glucose regulation was a predictor of cognitive performance. Additional data collected via a lifestyle questionnaire, found an association between the risks of developing poor glucoregulatory control and poor dietary habits, such as high-sugar carbohydrates. A limitation of this study may be that participants' glucoregulation measures were assessed from samples taken during each of three test visits (placebo, 25g glucose dose and 50g glucose dose), and may not be an accurate assessment of glucoregulation as a gold standard OGTT test was not conducted (see section 1.2.3 for a description).

A 2015 study which explored episodic memory differences in healthy young adults versus healthy older adults, used a dual task paradigm to examine effects of glucose and glucoregulatory control, with and without the extra cognitive burden of a mouse tracking task (Macpherson et al., 2015). Recognition response speeds and tracking performance of older but not younger adults were enhanced by glucose. Older participants, who had poorer glucose tolerance, as determined by OGTT incremental area under the curve(iAUC) appeared to have been preferentially targeted by glucose facilitation, which may be indicative of age-related differences in glucoregulatory control. The authors suggest that rather than offering support for hippocampal involvement, these results appear to suggest that in this cohort of healthy older adults, attentional resources are preferentially targeted by glucose. Structural evidence for these age-related effects of glucose administration was seen for this postulation in an MRI study conducted by the same research laboratory (Peters, White, Cornwell, & Scholey, 2018). Participants were younger and older healthy adults who underwent cognitive testing following glucose and placebo treatments at two test visits. The structural focus was on resting state functional connectivity of the hippocampus and there was a distinct age specific dissociation in glucose effects by age. This dissociation also extended to the cognitive tasks. The authors suggest that glucose administration can attenuate cognitive performance decrements in a cohort of older adults who have age-related impairment in glucoregulatory control, and that acute glucose was selectively targeting the posterior hippocampus.

Populations with Challenged Glucoregulatory Control

Evidence from behavioural recognition studies suggest that ingested glucose enhances cognitive performance but preferentially targets populations with poorer glucoregulation, such as healthy older adults for whom a decline in glucoregulatory control is considered a normal function of aging (Riby, 2012). A facilitative effect of glucose administration has also been observed in individuals with mild cognitive impairment (Riby et al., 2009). Ingested glucose has also been seen to facilitate episodic memory, but not sustained attention, in healthy older adults and also in older adults with MCI, whose blood glucose levels were approaching 'impaired fasting glucose' levels (see section 1.2.3 for a description) (Riby et al., 2009). However, whilst these findings have value, glucoregulatory control was assessed from a baseline sample after only a 2-hour fast, rather than an OGTT glucose tolerance test (see section 1.2.3. for details). Improved cognitive performance following an acute oral glucose dose of 75g has also been observed in populations where poor glucoregulatory control is often co-morbid, such as a study of patients with Alzheimer's disease (Manning, Ragozzino, & Gold, 1993). This study found that improved performance of tasks assessing orientation, word recognition

and recall, narrative prose, and face recognition was observed following glucose administration. Improved symptoms (memory) of dementia in individuals with Alzheimer's disease has been seen after elevating blood glucose levels via an intravenous infusion of glucose (Craft, et al., 1996).

There is also a postulation that facilitative effects of glucose are seen in tasks which evoke an increase in cognitive demand, such as when the study design utilises dual task paradigms. For example, hand movement sequences or mouse tracking tasks during the learning phase of episodic memory tasks (for a detailed description of the cognitive demand theory see section 1.5.2.6.1.1.). Scholey et al. (2013) found support for this hypothesis in a within-groups behavioural study which found no effects of glucose on either recollection or familiarity in healthy young adults (age range 18–35 years; mean age not reported). This study found that overall memory performance was enhanced by the 25g glucose dose when a 'high effort' hand-movement motor task was executed during the word display phase, implicating that the glucose facilitation was driven by task demand. Conversely, for the 'low effort' word display, overall memory performance was reduced following glucose compared to placebo. The authors argued that this suggested that task difficulty is a more important factor, supporting the task demand hypothesis rather than hippocampal mediation of the glucose effect (for a detailed view of the hippocampus hypothesis see section **Error! Reference source not found.**). Other studies which employed a dual task paradigm and found facilitative effects of glucose for episodic memory tasks include a between-groups design following a 25g glucose dose (Foster et al., 1998b); a between-groups design and after a 25g glucose dose (Sünram-Lea, Foster, Durlach, & Perez, 2001); a between-groups design and following administration of 75g of glucose (Awad, Gagnon, Desrochers, Tsiakas, & Messier, 2002); a between-groups design following 25g of glucose (Sünram-Lea, Foster, Durlach, & Perez, 2002); using a within-groups design and a cohort of slightly older adults (age range = 18-52, mean age 38.4) following a 25g dose of glucose (Meikle et al., 2004); again in slightly older adults (mean age 38.4 years) a between-groups design and following both 25g and 50g doses of glucose, participants were divided into 'older' and 'younger' groups with the greatest memorial advantage being seen for older adults, and for the highest cognitive load condition (Meikle et al., 2005). Taken collectively, this body of research supports the view that glucose enhancement of episodic memory is modulated by task demand (see section **Error! Reference source not found.**. for a detailed description of this hypothesis). This thesis will further explore the impact of task demand by exerting various levels of cognitive demand and utilising Tulving's (1985) Remember/Know paradigm to establish whether glucose is targeting recollection or familiarity memory processes.

Other studies have reported that glucose enhancement is moderated by glucoregulatory control (see section 1.5) which is commensurate with the view that glucose preferentially targets individuals with poor or impaired glucoregulation. Messier (2004) suggested that glucose enhancement of memory is symbiotic with pre-existing memory deficits. Evidence of glucose facilitation targeting poorer glucoregulators was found by Owen et al., (2013) who suggest that following a 25g glucose load, poor glucoregulatory control was a predictor of accuracy for a word recall task. Additionally, better regulators had poorer recall following glucose compared to placebo. Further episodic memory studies provide evidence for the mediating effect of glucoregulatory control in healthy young adults, whose glucose tolerance was within the normal healthy range, support the postulation that ingested glucose preferentially targets individuals with poorer glucoregulatory control (Benton, Owens, & Parker, 1994a; Craft, et al., 1994; Messier, et al., 1999). Messier et al. (2011) found an association between glucoregulatory control and verbal memory performance, and moreover that these decrements are observable in young non-diabetic adults. The association between obesity and poor glucose tolerance was also evident from an episodic memory study of young, non-diabetic heathy adults (mean age 24.62 years; mean BMI 25.7, BMI range: 18 - 51.7), of whom 24 were overweight or obese (Cheke et al., 2016). The authors found that there was a significant negative relationship between episodic memory task performance and higher BMI. The complex relationships between age-declining glucoregulatory control, memory deficits and glucose administration, also support the argument that poor glucoregulation is a contributing factor to episodic memory decrements (for reviews see Lamport, et al., 2009; Reche, 2020).

The overall view gleaned from the previously presented evidence is that there is a limited amount of behavioural evidence for the facilitative effect of glucose administration on episodic memory in young healthy adults but as such, some evidence does exist. Potential explanations for the lack of glucose effects may be due to study methodology. For example, because between-groups designs are comparing the effects of glucose versus placebo across two groups of participants, other confounding factors such as individual differences in memory may exist. Conversely, a within-groups design in which participants act as their own control, by being assessed under both experimental conditions are more robust and less susceptible to confounds. Secondly, population issues may arise from the fact that the majority of young adults participating in these studies are university students, which may be creating a ceiling effect, which may not be present in studies employing older adults from the general population. Finally, and the most attractive explanation, is that in a population of

young-healthy adults, that any effects of glucose may be too nuanced to be detected in behavioural studies.

The evidence above demonstrates that the effects of acute glucose administration differ by age, implying that glucoregulatory control has an impact on glucose facilitation.

1.5.2.7 Emotional Enhancement of Episodic Memory

The emotional enhancement hypothesis posits that, compared to neutrally valenced stimuli, emotional stimuli attract increased attention and evoke broader cognitive processing resources. One potential mechanism for this enhancement, which is pertinent to this thesis, proposes that emotional arousal evokes an increase in blood glucose levels, and in turn cerebral glucose levels. A study which demonstrated that emotionally valenced pictures and narrative improves memory found a +6% increase in blood glucose in fasted individuals following a saccharin placebo treatment (Parent et al., 1999). These significant effects were not however repeated following a 50g dose of glucose In a later study, Scholey et al. (2006), explored the effects of emotionality on circulating blood glucose levels, using neutral and negatively valenced stimuli in a word recall task. No glucose dose was administered in this study and the authors found that blood glucose levels were elevated for emotional words compared to neutral words at post-test, although no memorial advantage was seen for the emotional words. A between-subjects study asking participants to rate the arousal rating of either neutral or emotionally valenced pictures, found that the group who were rating the emotional pictures, correctly recalled more pictures and also had higher circulating blood glucose levels (Blake et al., 2001). Given that the hippocampus is heavily populated with insulin receptors and involved in the encoding and retrieval processes of episodic memory, it may be that the memorial advantage conveyed by emotionally valenced stimuli is driven by this elevation of glucose levels brought about by the increased demand required for the attentional resources involved in processing emotional stimuli.

1.6 Neurological Impact on the Neural Correlates of Recognition Memory

The mixed results across the behavioural literature in terms of the impact of an individual's glucoregulatory control, or an acute glucose dose on episodic memory are inconclusive. Chapters 4 and 5 further explore these effects from a neurophysiological perspective via exploratory event-related potential (ERP) investigations. Expectations being that in the absence of behavioural

evidence, more nuanced neurological differences between glucoregulatory groups or acute ingestion of a glucose dose may be detected.

Functional imaging methodologies include non-invasive data collection techniques which can provide spatial and temporal mapping of neural activity. More recent and more complex modalities such as fMRI, reflect hemodynamic monitoring of the blood flow and measures of blood oxygen levels. However, whilst fMRI monitoring allows for the acquisition of excellent spatial information, it lacks temporal accuracy. Temporal resolution defines the accuracy of the precise time (or latency) that responses are made to cognitive functions, such as responses to visual stimuli. The superior temporal resolution of electroencephalography (EEG) makes this method of data collection more suitable because it allows the underlying neural activity associated with cognitive function in the brain to be time-locked to the triggers in the cognitive testing programme (He et al., 2011).

An ERP recognition study (Scholey, et al., 2014) which manipulated cognitive load with a tracking task conducted on healthy older adults (Mean age 69.33 years), provided no support for glucose enhancement of recognition memory under task demand but suggested evidence for hippocampal mediated glucose effects on recollection in this older population. Structural evidence of glucose preferentially targeting older populations was seen in a recent fMRI study (Peters, et al., 2018). Analysis of resting state functional connectivity (rsFC) found increased connectivity between the posterior hippocampus and the medial prefrontal cortex following glucose ingestion, whereas younger participants were seen to have decreased connectivity. Conversely, an earlier ERP recognition study which investigated the neural correlates of recollection and familiarity in healthy young adolescents (Mean age 14.4 years) found that both recollection and familiarity were enhanced by a glucose dose suggesting a more global enhancement (Smith et al., 2009). However, Smith et al. stress that age may have been a possible limitation of this study, highlighting previous ERP research which found that frontal old/new effects are not seen in children (Smith, Riby, Sünram-Lea, van Eekelen, & Foster, 2009).

As there is a paucity of research which has directly investigated the neural correlates of episodic memory alongside glucoregulatory control, the ERP investigations in this thesis will approach the analysis from an exploratory standpoint which will aim to highlight potential early neurological differences in ‘better’ and ‘poorer’ levels of glucoregulatory control in a population of young, healthy, non-diabetic adults.

1.6.1 Event-Related Potential Components Associated with Recognition Memory

Event-related potentials (ERPs) are derived from electroencephalography (EEG) recordings, which measure minute electrical signals detectable from the scalp, indicative of neural activity. To derive ERPs related to memory processes, we average EEG signal for like-trials (e.g., remembered versus know trials). ERP investigations are used to gather brain activity data following an 'event' such as the presentation of verbal stimuli. Data is captured during specific time locked points dictated by the chosen ERP components. The ERP components used in the analyses in this thesis will be selected from *a priori* literature which have previously been seen to be sensitive to recognition memory processes or glucoregulatory control. During the encoding phase the selected components were the P1, N1, P3 and Late Positive Component (LPC) and for the analysis of the recognition phase the FN400 and the LPC components were assessed. In terms of recognition memory retrieval processes there is a paucity of neurophysiological research which directly encompasses episodic recognition memory processes and glucoregulatory control, where direct comparisons in the literature cannot be found, the manipulation of other types of stimuli have been discussed in the component descriptions below. However, it must be noted that ERP effects are not universal across different types of stimuli. Event related potentials are affected by the manner in which the stimuli are presented and as such, possess a 'physical stimulus confound' which precludes direct comparison, for example, between stimuli which have been presented verbally, audibly or graphically (Woodman, 2010). Where there is evidence that ERP components are sensitive to other recognition processes, the possibility that components may also be sensitive to episodic memory processes will be explored in this thesis.

Table 1.3 ERP components selected from *a priori* research in the recognition memory literature.

Analysis	Component	Latency Range
Encoding	P1	50 – 170 ms
	N1	165 – 220 ms
	P3	300 – 500 ms
	Late Positive Component	400 – 800 ms
Recognition	FN400 – Old words / New words	300 – 500 ms
(Accuracy)	Late Positive – Old words / New words	400 – 800 ms
Recognition	FN400 - Remember / Know	300 – 500 ms
(Subjective Judgements)	Late Positive - Remember / Know	400 – 800 ms

1.6.1.1 Encoding Phase Components

P1 Component

The P1 component, which is associated with early attentional effects, is the first positive deflection which occurs at about 100ms post stimulus. At the time of writing, studies have been reported which investigated the effects of glucoregulatory control on the P1 component during encoding phase of episodic memory, specifically, in a population of young, healthy non-diabetic adults. Previous research investigating the effects of aging on the early stages of face perception has suggested that greater P1 amplitudes are seen in older adults compared to younger adults (Gao, et al., 2009). A further study, focusing on older non-diabetic adults who had been identified as 'good' or 'poor' glucoregulators via an oral glucose tolerance test, found behavioural evidence for greater accuracy among better regulators but no glucoregulatory control effects were seen on the P1 component (Jones, Riby, & Smith, 2018). Whilst this greater P1 effect may be due to aging related glucoregulatory decline, it may be extrapolated that this effect may also be seen in younger non-diabetic adults.

N1 Component

The N1 component, which occurs at around 150 to 200 milliseconds post-stimulus, is elicited principally in posterior regions by visual stimuli and is associated with attentional effects. The N1 is the first component for which larger amplitudes are more negative. A study exploring the effects of unpleasant, neutral and pleasant pictures reported that the N1 was the earliest ERP component which responds to emotional manipulation with an enhanced N1 seen for both unpleasant and pleasant pictures relative to neutral pictures (Foti et al., 2009). Conversely, a further study found an enhanced left and right posterior N1 when reading emotional adjectives but no significant effect of valence (Herbert et al., 2008). In individuals with schizophrenia a diminished N1 has been identified during encoding of verbal material, however differentially from healthy controls, this smaller N1 was a predictor of better recognition (Longenecker et al., 2018).

P3 Component

The P3 component is reported to represent the processing of stimuli and as such, is implicated in working memory (Polich, 2007). A study investigating working memory in young adults Vs older adults noted that the P3 was sensitive to age-related changes (Peltz et al., 2011). Whilst the Peltz et

al. study did not consider glucoregulation, tentatively in relation to this thesis, age-related cognitive change is linked to challenges in glucose tolerance. Speculatively, glucoregulation differences in young adults may also manifest as differential P3 amplitudes. Previous research has identified the P3 component as being sensitive to the detection of comorbid changes in the auditory cortex in T2DM individuals, identifying neurological differences which showed a relationship between glycaemia and both the amplitude and the latency of the P3 component, in a cohort of both diabetic and non-diabetic individuals of both genders with an age range of 7 to 71 years (de Freitas Alvarenga et al., 2005). A further study separated the P3 into two sub-components, as such the P3a was associated with attention and the P3b was believed to reflect memory storage processes (Riby et al., 2008). Riby et al. found that P3b was sensitive to glucose ingestion with reduced amplitudes seen following glucose compared to placebo in response to a visual three-stimulus oddball task. A study exploring P3 latency found that T2DM individuals, aged between 38 and 75 years without cognitive impairment who were non-insulin dependent (NIDDM), had significantly later P3 latencies than did age-matched non-diabetic controls (Hissa et al., 2002).

LPC Component

The late positive component (LPC) is a positive going ERP component which is characterised as an enhanced positivity occurring at 400 to 800 ms post stimuli. This ERP component is believed to be a significant index in both the encoding and retrieval phases of memory (Olichney et al., 2011) The majority of research investigating the LPC is concerned with the retrieval of recognition memory. However, in a study involving emotionally valenced words, it was observed that the LPC responds differentially when the response is an automatic response to previously unseen words or 'new', or a reflective response to 'old' words that have been previously studied (Imbir et al., 2015) . The late positive component has shown sensitivity to the emotional valence of pleasant and unpleasant words, pictures and faces when compared to neutral items (Hajcak et al., 2012) with greater LPC amplitudes elicited by unpleasant, compared to pleasant pictures (Weinberg & Hajcak, 2010).

1.6.1.2 Recognition Phase Components

FN400 Component

The FN400 component is a positive going ERP component which is characterised as an enhanced positivity occurring at 300 to 500 ms post stimuli. Early evidence for dual-process models of recognition memory argues that recollection and familiarity are two distinct processes (for a review see Yonelinas, 2002). Some ERP studies of recognition memory purport that familiarity and

recollection are indexed by the FN400 and the LPC components, respectively. The FN400 is distinguished as a frontal effect that is seen to be more negative for new, previously unseen verbal stimuli (Curran, 2000; Danker et al., 2008; Stróżak et al., 2016; Woodruff et al., 2006a).

There is, however, theoretical debate which questions the dual-process model's identification of familiarity and recollection as two distinct processes. The opposing view is that recognition is in fact a single-process model, and proposes that rather than two distinct processes, familiarity and recollection are in effect a continuum reflecting memory strength. Support for this interpretation has been seen in a study which demonstrated that participants' subjective confidence judgements were reflected in increases in FN400 amplitudes (Woroch & Gonsalves, 2010). In terms of the FN400, this thesis will further explore this question with an assessment of amplitudes for 'old' and 'new' words. Additionally, Tulving's (1985) 'remember or know' paradigm will be applied to correct recognitions of previously seen 'old' words. It is proposed that increased FN400 positivity for responses to these correct recognitions will be indicative of memory strength. In terms of the impact of glucoregulatory control on recognition memory, previous research has suggested that non-diabetic older individuals (Messier, et al., 2003) and younger individuals (Messier, et al., 2011) have been shown to exhibit cognitive impairment prior to reaching the pre-diabetic stage of glucoregulatory control. The current research will investigate whether early indication of these impairments can be extrapolated to and are detectable in FN400 amplitudes.

LPC Component

A further ERP component associated with recognition memory is the positive going LPC component which is characterised as an enhanced positivity occurring at 400 to 800 ms post stimuli. Viewed through the lens of the dual-process model of memory the LPC is believed to represent the process identified as the explicit recollection of previously studied stimuli. Old and new manipulations of recognition memory have suggested that LPC amplitudes localised over the posterior region are increased for recollections of previously seen stimuli compared to old items which no recollection occurred (Curran, 2000; Rugg & Curran, 2007). Conversely, support for the single-process continuum model was found in a study which identified larger a LPC for 'remember' decisions than for 'know' decisions (Leynes & Phillips, 2008). Whilst it is well known that a decline in explicit memory is commensurate with normal healthy aging and impaired glucose tolerance (for a review see Lamport et al., 2009) there is, to the time of writing, scant research which explores the concept of the impact of poor glucoregulatory control on the neural correlates of episodic memory. The investigation of

ERPs, specifically the LPC component, may give early insight into the potential impairment of explicit recollective memory relative to poor glucoregulatory control.

1.7 Summary of Thesis Rationale, Aims and Objectives.

With the growing global prevalence of T2DM and the co-presenting cognitive impairments that often accompany this pervasive disease, there is growing pressure to augment early interventions which may prevent individuals from progressing to a clinically diagnostic level of glucose intolerance. T2DM is both preventable and reversable when individuals make healthy lifestyle choices. This introductory chapter has discussed the cognitive and cardiovascular impact of glucose administration and glucoregulatory control relative to both healthy individuals, and those populations who are at risk of, or co-present with impaired glucoregulatory control. Several methodologies will be employed to explore the impact of glucose administration and glucoregulatory control and investigate whether early markers of risk for T2DM are detectable in a cohort of young healthy non-diabetic adults who have self-reported that they are free from any glucoregulatory or metabolic disorders, such as diabetes, and without heart rate disorders such as arrhythmias. One of the principal objectives of this research is to explore the impact of glucose administration and glucoregulation on a cohort of healthy young non-diabetic adults to investigate whether early cognitive changes can be associated pre-clinical blood glucose levels and with risk factors for developing T2DM. Identification of early cognitive change may help to establish a profile of T2DM risk, based on the multiple methodologies employed in the experimental chapters.

The concept of using multiple methodologies to build this risk profile will create a broader and more robust pre-clinical indication of the potential pathologies which can co-present with T2DM. Exploring multiple diagnostic avenues may lead to identification of at-risk individuals prior to more advanced cognitive decline being evident than was previously assessed by a traditional OGTT investigation of blood glucose levels (see section 1.2.3). Early recognition would also mean that individuals who are found to be at risk, can be directed toward interventions which will potentially prompt them into taking steps, such as implementing lifestyle choices, to prevent themselves from developing T2DM. The aims and objectives of the individual experimental chapters are summarised below in section 1.7.1.

1.7.1 Experimental Chapter Rationales, Aims and Objectives

Four studies were conducted to investigate the overall aims and objectives of this thesis. These are set out below and principal aims are stated (details of specific chapter research questions can be found in the experimental chapters).

Chapter 2: 'An Assessment of the Efficacy of Non-Nutritive Sweeteners and Flavour Masks Used in Experimental and Placebo Drinks.'

Objectives: This chapter seeks to clarify whether the mixed results of studies exploring the impact of glucose administration may be modulated by the experimental and placebo drink ingredients which are assumed to be inert. To investigate the potential effects of commonly used treatment ingredients in isolation, with a view to identifying the most appropriate drink compositions for cognitively and calorifically inert placebo treatments. The secondary aim was to explore the effects of a standard 25g glucose dose in its pure form, without the potentially active effects of other added ingredients. Additionally, chapter 2 explores the impact of glucose and non-nutritive placebo across a range of cognitive domains to ascertain whether glucose preferentially targets specific cognitions.

Chapter 3: 'Investigation of Combined Treatment Ingredients: Does Glucose Administration Mediate Episodic Memory and Inhibition Processes?'

Objectives: This chapter explored the potential effects of these treatment ingredients in the combinations commonly used in the glucose enhancement literature. The conclusions drawn informed the choice of treatment ingredients used in the remaining studies included in this thesis. The secondary aim was to investigate glucose facilitation of episodic memory for neutral and emotionally valenced words and pictures, and sustained attention. This chapter further informed the choice of drink ingredients to be used in Chapters 3 and 4 of this thesis.

Chapter 4: 'The Influence of Ingested Glucose and Glucoregulatory Control on the Neurophysiological and Physiological Correlates of Episodic Memory and Inhibition in Young Non-Diabetic Adults'

Objectives: Chapter 4 investigated the role of glucose and glucoregulatory control on; episodic memory for neutral and emotional words, and sustained attention. Previous behavioural research has produced mixed results in terms of the impact of glucose administration on healthy young

adults. It may be that in this population effects of glucose ingestion are too nuanced to be detected in behavioural data. Additionally, glucoregulatory control may also be a factor in how glucose administration impacts on cognitive performance. To explore this notion, participants were identified as better and poorer glucoregulators via a median split based on their measures of iAUC. This chapter sought neurophysiological evidence as to whether glucoregulatory control and/or glucose ingestion were modulating recognition memory. Word recognition tasks were employed to elucidate the two contesting theories of glucose facilitation, namely the 'task domain' and the 'task demand' hypotheses. Cardiovascular issues are commonly reported in individuals who present with conditions such as T2DM which involve poor glucoregulation. This chapter additionally explored the physiological impact of glucoregulatory control and/or glucose ingestion of cardiovascular measures (ECG heart rate beats per minute) to ascertain whether early cardiovascular differences were apparent in this population.

Chapter 5: 'Investigating the Impact of Elevated Type 2 Diabetes Risk on Episodic Memory Processes and Inhibition: Specifically Comparing Neurophysiological, Glucoregulatory and Cardiovascular Factors in Non-Diabetic Healthy Young Adults Vs Potentially at Risk Young Adults.'

Objectives: Chapter 4 found evidence to suggest that glucoregulation and treatment effects were evident in the more nuanced neurophysiological data. This chapter sought to investigate whether the relationships between glucoregulation, the risk factors for developing poor glucoregulation (and consequentially T2DM) are already apparent in a cohort of young healthy non-diabetic adults. This chapter investigated whether early pre-clinical levels of poor glucoregulatory reflected an individual's risk of developing T2DM. Aiming to establish whether these early decrements in glucoregulatory control, are correlated with known T2DM risk factors. Measures of glucoregulation and glucose administration were employed to investigating whether challenged but non-clinical glucoregulation in healthy young adults is evoking differences in episodic memory and attentional resources, and as such, is potentially an early marker for risk of T2DM. Additionally, this chapter investigated the impact of glucoregulation and glucose administration on measures of heart rate variability to explore whether early indications of cardiovascular problems, which are often comorbid with T2DM, are detectable in the current population.

2 An Assessment of the Efficacy of Non-nutritive Sweeteners and Flavour Masks used in Experimental and Placebo Drinks.

2.1 Introduction

In view of the inconsistencies across the glucose enhancement of episodic memory literature, this chapter set out to investigate potential confounds in the methodology involved in administering acute experimental and placebo treatments (see section 1.5.2.6.1.2 for more details of studies).

The non-nutritive sweeteners used in placebo treatments and the flavour-masking agents, employed in both placebo and experimental treatments, are assumed to be cognitively inert. Close inspection of the ingredients of the treatments used across the glucose enhancement literature revealed, considerable variation of ingredients, quantities of additives and drink volumes, for examples see Table 2.1. As the ingredients are assumed to be cognitively inert, this is perhaps not surprising. However, these inconsistencies across the literature may be underpinned by the differences within the treatments employed, potentially masking, or modulating the reported glucose facilitation effects.

This muddled picture may be the result of the placebo employed as opposed to a direct glucose effect. Some studies report cognitive facilitation following glucose consumption in relation to an aspartame placebo, when assessing episodic memory (specifically recognition memory) or attention and response inhibition (Brandt, Gibson, & Rackie, 2013; Smith & Foster, 2008; Smith, Riby, Sünram-Lea, van Eekelen, & Foster, 2009; Sünram-Lea, Dewhurst, & Foster, 2008). Other studies report variable and often contradictory effects of glucose ingestion when assessing these domains using similar methodologies but with a saccharin placebo (Ford, Scholey, Ayre, & Wesnes, 2002; Messier, Awad-Shimoon, Gagnon, Desrochers, & Tsiakas, 2011; Scholey, MacPherson, Sünram-Lea, Elliott, Stough, Kennedy, et al., 2013; Scholey, Sünram-Lea, Greer, Elliott, & Kennedy, 2009). There is evidence that aspartame, a non-nutritive sweetener commonly used in placebo treatments, can influence cognition and circulatory blood glucose. A high, but well below acceptable maximum intake, aspartame diet for eight days was seen to influence neurobehavioural health (Lindseth et al., 2014). Participants experienced increased irritability, more depression, and worse performance on spatial orientation tests. Additionally, whilst no significant differences were seen overall for working memory, two participants displayed impaired working memory performance. This suggests that

aspartame may elicit detrimental effects in some participants; although it was unclear which factors may have been underlying this effect. A further study explored the memory of chronic, versus non-users of aspartame in a sample of students, finding that aspartame users reported longer memory lapses than non-users (Konen et al., 2000). High levels of aspartame may also alter blood glucose levels. Melanson et al. (1999) found that a calorie-free, aspartame sweetened drink evoked declines in circulatory blood glucose levels in 40% of subjects, increases in 20%, and stable levels in the remaining in 40%. These post-ingestive variations in blood glucose levels correlated with participants' perception of drink sweetness and predicted their subsequent food intake, suggesting that sweet taste receptors in the mouth may be responding to aspartame ingestion. However, Rogers (2013) showed that ingestion of aspartame (capsulised and dissolving in the gut, hence in flavourless form) induces an anorectic response in participants. Interestingly, there is mixed research in terms of the effects of carbohydrate mouth rinsing on both exercise performance and brain activity. One study which explored the impact a 6.4% glucose or saccharin containing placebo mouth rinses, found that cycling time trials were completed more quickly following the glucose mouth rinse compared to placebo (Chambers et al., 2009). Additionally, using fMRI, the authors also found that glucose but not saccharin mouth rinsing activated reward related brain areas. However, a more recent study, using a carbohydrate versus placebo design, argues that carbohydrate mouth rinsing had no behavioural or neurological effects on cognitive processes (Chandler et al., 2020).

An alternative explanation for the effects of aspartame on cognition may be via its potential to influence insulin production, (for a more detailed explanation of the role of insulin see section 1.2.1). There is a growing body of research which implicates the use of non-nutritive sweeteners as contributing to insulin resistance via a gut microbiota pathway. It has been shown that artificial sweeteners such as saccharin, aspartame, and sucralose can cause perturbations in the gut microbiota which have the potential to disrupt metabolic health, leading to insulin changes (for a review see Nettleton et al., 2016). Furthermore, evidence for the impact of gut microbiota perturbations on insulin sensitivity was seen in a human study in which males with metabolic disorder received faecal microbiota transplantation from lean donors. The recipients were seen to have improved insulin sensitivity after six weeks (Kootte et al., 2017).

Further evidence that aspartame may influence brain chemistry comes from animal studies. After aspartame administration at 5.625 mg/kg, mice were found to have significantly impaired performance on the water maze test with concentrations of brain glucose decreased by 25.8% (Abdel-Salam et al., 2012). A further animal study, exploring memory and the neurotropic effects of

aspartame, found significantly higher levels of cellular apoptosis in the hippocampus of mice after aspartame administration for 32 days (Villareal et al., 2016). The above studies demonstrate that these changes in cognition are occurring following both acute and longer-term ingestion of aspartame. However, whilst these animal studies do provide support for the line of research which suggests the potential of aspartame to facilitate changes in cognition, the neurobiological changes due to aspartame observed in animal models cannot yet be generalised to the glucose enhancement literature. Such evidence suggests that aspartame in sweetness matched placebo treatments may not be inert, and as such may influence the reported changes in cognitive functioning when comparing non-nutritive aspartame placebo treatments with glucose.

Another non-nutritive sweetener commonly employed in placebo treatments is saccharin. Although extensively tested since the 1970s, at the time of writing there are no studies reporting saccharin related cognitive or neurobiological changes in the literature. This potentially makes saccharin a more viable non-nutritive sweetener for use in placebo treatments. One potential explanation for this may be that, unlike aspartame, saccharin does not have the capacity to influence insulin levels because it is not metabolised in the gastrointestinal tract (Ucar & Yilmaz, 2015).

In addition to the differences in non-nutritive sweeteners employed in placebo treatments, there are also inconsistencies in the flavour masking agents which are used. Some studies did not add flavour masking agents and simply add glucose or non-nutritive sweeteners to plain water (Brandt, Sünram-Lea, Jenkinson, & Jones, 2010; Brandt, et al., 2006; Smith, et al., 2009; Sünram-Lea, Foster, Durlach, & Perez, 2002; Sünram-Lea, et al., 2002). Where employed, they are utilised to limit participants' ability to identify whether they have consumed glucose or the placebo treatment.

Lemon juice is commonly used for this purpose in both experimental and placebo treatments (Brandt, Gibson, et al., 2013; Gagnon, et al., 2012; Sünram-Lea, et al., 2008). However, in terms of the efficacy of lemon juice as a cognitively inert treatment ingredients, there is evidence which suggests that citrus juice can potentially affect cognitive processes (Alharbi et al., 2015; Bell et al., 2015; Kean et al., 2015). One possible explanation for this may be that cognition may be influenced by the potential of flavonoid-rich fruits, such as citrus. Whilst flavonoids may have a protective influence and long-term consumption has been shown to protect against age-related decrements, specifically memory and cognitive decline (Spencer, 2010; Spencer, Vauzour, & Rendeiro, 2009; Williams & Spencer, 2012). However, it is unlikely that the flavonoid content of the acute doses of 10 ml of lemon juice or RSFOC to be used in the current study would have any immediate impact on

cognition. Lemon juice may also facilitate cognition via a perceptual effect known as 'refreshing perception'. Labbe et al. (2011) utilised a three-treatment crossover design in which participants were given a 70 g optimised citrus flavoured water ice served at -17 °C, a standard water ice also served at -17 °C or a 70 ml glass of water which was served at 7 °C. Following consumption of frozen water optimised with citric acid, changes were observed in mental energy, specifically in subjective measures of alertness; improved attention and improved cortical activation in the alpha and beta ranges were also seen (Labbe et al., 2011). It is also known that refreshing or cooling sensations are mediated by receptors located in trigeminal cold-sensing neurons (Patapoutian et al., 2003), evoking increases in physiological arousal and raising levels of cortical activation (Eccles, 2000), i.e., a perceptual effect of refreshment. To be clear, this previous research provides pertinent evidence that lemon juice can potentially influence cognition, yet the neurobiological processes that underpin these effects remain unclear.

The temperature at which experimental drinks are consumed may be another confound, there is no uniform consensus across research centres, with drinks being served at varying temperatures. Research has found that hypothalamic activity, which is associated with increased satiation, was lowered following glucose at both 22^{o}C and 0^{o}C, and water at 0^{o}C (Van Opstal et al., 2018); conversely, water at room temperature increased activity in the hypothalamus. Considering this impact on the hypothalamus, a recent rodent study detected content-specific signal routing by the hypothalamus was involved in modulating hippocampal memory processes (S. Chen et al., 2020). These findings highlight the importance of consistency in the serving temperatures of experimental drinks. A further consideration is the volume of drinks which is also inconsistent across studies (see Table 2.1 for examples). Volume sensing and appetitive hormones such as ghrelin which are found in the intestinal tract are reported to modulate memory (Atcha et al., 2009). As with treatment temperatures, to allow for consistency across the studies, all drink volumes included in this thesis will be a total volume of 200 mls, i.e., after inclusion of treatment ingredients drinks will be made up to 200 mls.

Robinsons No Added Sugar Orange Cordial (RNASOC) has also been commonly used as a flavour-masking agent in both glucose and placebo treatments (Kennedy & Scholey, 2000; Macpherson, et al., 2015; Scholey, MacPherson, Sünram-Lea, Elliott, Stough, & Kennedy, 2013; Scholey, et al., 2001). This flavour masking agent contains a combination of aspartame and saccharin, potentially challenging its validity as an inert flavour masking agent, as per the earlier consideration of the influence of non-nutritive sweeteners. In the glucose enhancement literature RNASOC is utilised in

both experimental and placebo treatments see Table 2.1 for examples. It is possible that the use of flavour masks such as RNASOC may be influencing the reported findings, as it may modulate evoked changes in glucose absorption into the blood. Blood glucose peaks at approximately 45 minutes post drink for simple glucose, and with glucose administered with saccharin. However, this peak is observed at 30 minutes post drink when glucose is administered with aspartame (Bryant, 2013). Whilst blood-glucose measures were not taken in the current study, the methodology employed ensured that post-treatment assessments for all conditions took place after the glucose dose had entered the bloodstream. The ten-minute post-ingestion absorption period employed here is commonly used in much of the literature (see Table 2.1 below for examples), although this is another area of inconsistency in the glucose literature, with absorption periods ranging from unspecified to 20 minutes. Although no combinations of treatment ingredients were used in this study, the temporal variation in glucose absorption potentially has critical implications for future work that may depend on the combination of additives in placebo and treatment conditions. Cognitive performance may differ across experiments using similar methodologies but with differing treatment ingredients due to differences in timings of peak blood glucose levels, therefore caution is needed when comparing studies. Aside from these temporal complications, clearly there is much evidence to suggest that some ingredients of placebo treatments used in the glucose enhancement literature may not be cognitively inert. Primarily exploring drink ingredients in isolation in this chapter will provide the basis for further exploration in chapter 3 of these compounds in combinations commonly used in the glucose literature.

Further differences in the glucose literature involve pre-test fasting periods which range from 'unspecified' and 'overnight' through to 13 hours (see Table 2.1 below). As participation in this research formed a part of their learning experience, participants were not asked to fast prior to testing. However, it was felt that it could be argued that knowing what effect the treatments were having whilst in their normal state is potentially as interesting and useful than in a laboratory-based setting where there is an artificial manipulation. i.e., someone who normally has breakfast versus someone who does not. In view of the fact that this study was collecting data for baseline pre-treatment measures, which is uncommon for between-groups studies in the glucose literature (see Table 2.1 below for details), and including these as a covariate, this would facilitate a robust evaluation of the effects of the treatments on participants in their natural state.

Acute glucose ingestion has been shown to facilitate cognitive performance on selected tasks (see section 1.5) which represent varying cognitive domains. To explore differences across these domains

this study will incorporate cognitive tasks which will assess any effects on episodic memory, attention and response inhibition, psychomotor performance cognitive demand, working memory attention and vigilance and executive function, see Figure 2.1 for a list of tasks and targeted cognitive domains.

The primary aim of this chapter was to begin to investigate the inconsistencies in the literature concerning the effects of glucose administration on cognitive processes. Differential findings have occurred across the various research centres, with some consistently finding an effect of glucose and others not. An additional consideration of studies in the glucose literature is the use of between-groups designs, with some studies not collecting baseline data as a control. Because of the number of treatments being examined in the current study it was necessary to use a between-groups design. Whilst this may not be as robust as a within-groups study design in which participants are acting as their own control, this was ameliorated by assessing all participants baseline scores and using ANCOVA to control for these. This chapter explored the potential effects of these commonly used treatment ingredients in isolation on a range of cognitive tasks. This chapter examined two non-nutritive sweeteners, aspartame, and saccharin: two flavour masking agents, RNASOC and lemon juice, as well as glucose and water only. All the above ingredients were delivered individually in water, and these would be compared to a water only control. Glucose has been seen to facilitate a range of cognitive domains (see section 1.5.2 for details of these. The secondary aim was to give insight into the effects of a standard 25g glucose dose in its pure form, delivered in water, without the potentially active effects of other added ingredients. This investigation of the impact of glucose on several targeted domains will pilot the choice of cognitive tasks to be implemented throughout the remainder of this thesis. Because of the number of treatments being examined it was necessary to use a between-groups design. Whilst this may not be as robust as a within-groups study design this was ameliorated by assessing all participants baseline scores and using ANCOVA to control for these. The research questions addressed by this chapter were as follows:

- Will glucose enhancement of memory effect be differentially mediated by differences in drink compositions (active and placebo)?
- Do the flavour masks commonly used in the glucose literature influence cognitive performance?
- Do so-called inert substances used in placebo drinks, such as saccharin or aspartame, produce differential effects?
- How does a standard 25g glucose dose, in its pure form impact cognition in comparison to each individual treatment ingredient ?

Table 2.1 Treatment and Methodology Examples. Showing the range treatment ingredients and quantities, and differences in methodologies used in studies investigating the effects of glucose on cognition.

Reference	Participants	Study Design	Cognition assessed at baseline?	Glucose dose (g)	Flavour-mask	Saccharin sweetened placebo	Aspartame sweetened placebo	Pre-dose fast (water allowed)	Pre-task absorption period (minutes)	Suggested Glucose Effects
Brandt, Gibson, & Rackie, (2013)	60 undergraduates (mean age = 19.7 years)	Between Groups	No	25	2 squirts lemon juice		5 x aspartame tablets	Overnight fasting	15	Speeded reaction times for congruent & incongruent 'Stroop' responses. No effect on error rates.
Brandt, Sünram-Lea, & Qualtrough, (2006)	40 healthy young adults (mean age = 22 years	Between Groups	No	25	None specified		5 x aspartame tablets	2 hours	15	The memorial advantage of emotion was not further facilitated by glucose.
Ford, Scholey, Ayre, & Wesnes, (2002)	20 healthy young adults (aged 20 to 23 years)	Between Groups	No	25	20 ml sugar-free orange cordial	28 mg		Overnight fasting	20	No effect of glucose on memory
Gagnon, Desjardins-Crépeau, Tournier, Desjardins, Lesage, Greenwood, & Bherer,(2012).	20 none-diabetic adults 60 yrs and older	Within Groups	Yes	50	10 ml lemon juice	23.7 mg		10 to 12 hours	15	Improved dual-task efficiency in older adults
Kennedy, & Scholey, (2000)	20 healthy adults (19 to 30 years)	Within Groups	No	25	25 ml Robinsons low Calorie Orange Squash	30 mg		Between 9 and 12 hours	20	No significant effect on word retrieval.
Macpherson, Roberstson, Sünram-Lea, Stough, Kennedy, & Scholey, (2015).	24 healthy young adults (18 to 23 years) and 24 healthy older adults (65 to 85 years)	Within Groups	No	25	Orange sugar-free cordial (unspecified amount)	30 mg		12 hours	Not specified	Enhanced response times for recognition memory and tracking accuracy during dual-task in older adults only.
Messier, Awad-Shimoon, Gagnon, Desrochers, & Tsiakas, M. (2011)	122 healthy young adults	Within Groups	No	50 (plus 4 mg of saccharin to match sweetness)	Lemon-flavouring (unspecified amount)	50.4 mg		Not specified	5	No effect on cognitive performance

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Messier, Desrochers, & Gagnon, (1999)	36 healthy adults (aged 19 - 34)	Within Groups	No	50 (plus 4 mg of saccharin to match sweetness)	Lemon-flavoured	50.4 mg	Not specified	Not specified	Enhancement of memory seen in those participants with poorer glucose regulation.
Owen, Scholey, Finnegan, & Sünram-Lea, (2013)	24 healthy young adults (aged 18 - 30 years)	Within Groups	No	0, 25, 60	Unspecified pharmacologically inactive flavourings.	Unspecified artificial sweeteners	12 hours	15	For 25 g dose there was improved immediate and delayed verbal declarative memory for poorer regulators.
Scholey, Harper, & Kennedy, (2001)	20 healthy adults (aged 20 to 30 years)	Within Groups	No	25	25 ml 'Summer Magic' no added sugar apple and blackcurrant squash	30 mg	9 to 13 hours	20	Improved performance on 'Serial 7's' but no effect on 'Word Memory Task.'
Scholey, Macpherson, Sünram-Lea, Elliott, Stough, & Kennedy (2013)	20 healthy young adults (18 to 35 years)	Within Groups	No	25	Robinsons Sugar Free Orange Cordial (unspecified amount)	30 mg	12 hours	10	Drink * Effort interactions but no effect on 'remember' or 'know' responses
Scholey, Sünram-Lea, Greer, Elliott, & Kennedy, (2009).	120 healthy adults (mean age = 21.6 years)	Between Groups	No	25	20 mls Robinsons Sugar Free Orange Cordial	30 mg	10.5 to 11 hours	20	Based on initial thirst; for less thirsty individuals glucose enhanced recall. Those more thirsty recalled fewer words following glucose than after placebo.
Smith & Foster (2008)	22 healthy adolescents (14 to 17 years)	Within Groups	No	25	None specified	5 x 'Equal' tablets (10% Aspartame)	10 hours	10	Enhancement of memory seen in those participants with better glucoregulatory efficiency.
Smith, Riby, Sünram-Lea, Van Eekelen, & Foster, (2009).	18 healthy adolescents (13 to 18 years)	Within Groups	No	25	None specified	5 x 'Boots' aspartame tablets	2 hours	10	Enhancement seen in both the recollection and familiarity components of recognition memory
Sünram-Lea, Dewhurst, & Foster, (2008)	56 healthy adults (18 to 25 years)	Between Groups	No	25	2 teaspoons of lemon juice	Unspecified artificial sweeteners	12 hours	15	Enhancement of 'recollection' but not 'familiarity' components of recognition memory.
Sünram-Lea, Foster, Durlach, & Perez, (2002)	80 healthy young adults (18 to 29 years)	Between Groups	No	25	None specified	5 x 'Boots' aspartame tablets	2 hours	Not specified	Enhanced memory when encoding alongside a secondary task. No effect when encoding without the secondary task.

2.2 Materials and Method

2.2.1 Design

A randomised, placebo controlled, single-blind between-groups design was employed. The variables were 6 x Treatment (Glucose/Saccharin/Aspartame/RNASOC/Lemon juice/Water) and 2 x Time (baseline and post-treatment).

2.2.2 Participants

One-hundred and thirty self-reportedly healthy adult volunteers (114 females, 16 males; mean age 22.59 years, SD 6.38) took part in this study which was approved by the Staffordshire University Psychology Ethics Committee. A power analysis conducted prior to recruitment suggested that this was more than adequate to achieve a power of 0.8. As participants were students and as such, participation in this research formed a part of their learning experience, it was not possible to predict numbers per group prior to the study. Additionally, students were awarded research participation credit. Procedures were in place so that all students could fully participate in the learning experience, even if they had food allergies, metabolic disorders or should they choose not to consent to the researcher utilising their data.

Prior to taking part in the study informed consent, and health and demographic screening was completed to ascertain whether prospective participants met the exclusion/inclusion criteria of the study. Participants were screened for food allergies relating to the treatments used in the study and any glucoregulatory/metabolic disorders e.g., diabetes, or phenylketonuria. All participants were asked to self-report whether they were in good health, free from prescription drugs (excluding contraceptives), over-the-counter medicines, illicit and recreational drugs (excluding nicotine). Participants were not asked to fast prior to testing and were assessed in their normal state. Of the 130 participants there were 29 smokers (mean 8.35 cigarettes per day, SD 4.38). Smokers were not asked to refrain from smoking on study days. Demographic and morphometric information collected indicated the number of years in education (mean 15.30 years, SD 1.24), and BMI (mean 26.63, SD 6.45). As this thesis would be exploring the effects of lifestyle choices on cognition there were no exclusion criteria based on participants' BMI. For a complete range of individual characteristics, please see

Appendix 2.1.

2.2.3 Treatments

The purpose of this chapter was to compare the individual ingredients of standard drink compositions utilised within this area of research. The treatment drinks consisted of common ingredients, which are typically found in everyday food/drink items such as energy drinks (e.g., Lucozade/glucose) and beverage sweeteners (e.g., Hermesetas - Saccharin). Participants were blind to their allocated condition but were fully informed as to the ingredients used in all drinks to be consumed over the study. All drinks were prepared on the day prior to testing and were stored in sealed containers overnight in a refrigerator prior to serving. All drinks had a total volume of 200 mls, i.e., after inclusion of treatment ingredients drinks were made up to 200 mls with the addition of plain water. The six experimental drinks are shown in Table 2.2 below.

Table 2.2 Experimental drink compositions (all drinks were 200ml in volume)

Treatments
25g glucose
5 saccharin-based sweeteners
5 aspartame-based sweeteners
20 ml Robinsons No Added Sugar orange cordial
10 ml lemon juice
water only

Health screening forms were checked for allergies prior to handing out drinks. The drinks were mixed and labelled by the researcher and randomly allocated to participants. Drinks were administered in sealed bottles, covered with paper sleeves to hide the contents. Participants were instructed not to discuss their drinks with other participants.

2.2.4 Assessments

COMPASS

The cognitive test battery used to assess performance was constructed using the Computerised Mental Performance Assessment System (COMPASS, Northumbria University, Newcastle upon Tyne, UK). COMPASS software creates a full set of randomised stimuli for every single assessment; this

ensured that both sets of tasks performed by each individual participant were different. The cognitive task battery was presented in the order shown in Figure 2.1 via desktop computers, apart from Word Recall, for which participants used pen and paper to record their responses. Performance data was automatically documented in an Excel results file. Reaction times throughout were measured in milliseconds. The duration of each of the test batteries was approximately 35 minutes.

Figure 2.1 Schematic of COMPASS computerised task running order.

Cognitive Task	Target Cognitive Domain
Bond Lader Mood Scales	
Physical and Mental State Scales	
Word Presentation	
Immediate Recall	Episodic memory
Picture Presentation	
Stroop Test	Attention/Response Inhibition
Simple Reaction Time	Psychomotor performance/Attention
Choice Reaction Time	Psychomotor performance/Attention
Serial 7's Subtractions	Working memory/Executive function
Rapid Visual Information Processing	Attention & Vigilance
Card Sorting	Executive Function
Delayed Word Recall	Episodic memory
Delayed Word Recognition	Episodic memory
Delayed Picture Recognition	Episodic memory
Bond Lader Mood Scales	
Physical and Mental State Scales	

2.2.4.1 Bond Lader Mood Scales

Subjective measures of mood were assessed at baseline using the COMPASS Bond Lader mood scales in which participants used the mouse to indicate the point on the scale which was indicative of how they were feeling. Bond Lader (Bond & Lader, 1974) measures were taken for how ‘alert’, ‘calm’ and ‘contented’ participants were feeling. Data was collected via 16 scales with antonyms at each end which was then compiled, as per author instructions, to create the three factors of alert, calm and content.

2.2.4.2 Physical and Mental State Scales

Subjective measures of physical and mental state were also taken at baseline using the COMPASS Visual Analogue. Again, participants used the mouse to indicate the point on the scale which was indicative of how they were feeling. Physical and mental state assessments were collected for participants' levels of 'mental energy', 'concentration', 'fullness', 'physical stamina', mental fatigue', 'hunger', 'mental stamina', 'physical tiredness', 'thirst', 'mental tiredness'.

2.2.4.3 Word Presentation

Fifteen randomised target words were presented on the screen for 1500 milliseconds with an inter-stimulus gap of 1000 milliseconds.

2.2.4.4 Immediate Word Recall (Episodic Memory)

Using the recall sheets provided, participants were given 60 seconds to write down as many of the words that they could remember. They were instructed to drop the recall sheet on the floor behind them when they had finished, and these were collected by the researcher. Scores were manually tallied by the researcher.

2.2.4.5 Picture Presentation (Episodic Memory)

Fifteen randomised of photographs of objects, buildings and scenes were presented individually on the screen. Participants were asked to remember each picture as they would be asked to recall these pictures later in the session.

Display time was 2 seconds, and the inter-stimulus gap was 1 second.

2.2.4.6 Stroop (Attention/Response Inhibition)

COMPASS delivered a computerised version of the Stroop Task (Owens et al., 1997; Stroop, 1935) which had been created to deliver randomly ordered congruent and incongruent presentations. Words describing colours (GREEN, BLUE, RED, YELLOW) were randomly presented in either congruent, when the text colour and the word were the same, or incongruently coloured text where the text colour was different from the word (e.g., BLUE was presented in RED text). Fifty stimuli were presented, and participants were instructed to use their mouse to select one of the relevant colour

boxes which were located on the right-hand side of the screen. Response reaction times and response accuracy was recorded for each of the tasks.

2.2.4.7 Simple Reaction Time (Psychomotor Performance/Attention)

Upward pointing arrows appeared at randomly varying inter-stimulus intervals on the screen. Participants were instructed to press the keyboard spacebar as soon as they saw the arrow. Fifty stimuli were presented for 1 second and the inter-stimulus gap ranged between 1 and 3.5 seconds. Mean RT was recorded.

2.2.4.8 Choice Reaction Time (Psychomotor Performance/Attention)

Arrows pointing either left or right appeared at varying inter-stimulus intervals on the screen. Participants were instructed to press either the right or the left direction keys on the keyboard as soon as they saw the arrow. Fifty stimuli were presented for 1 second and the inter-stimulus gap ranged between 1 and 3.5 seconds. Mean RT and accuracy (i.e., % of correct responses) were recorded.

2.2.4.9 Serial 7s Subtractions (Working Memory/Executive Function)

A random number between 800 and 999 was displayed on the screen and participants were instructed to subtract 7 from this number and enter their answer using the linear number keys at the top of the keyboard and then to press the 'Enter' key. The starting number then disappeared, and participants were instructed to continue to subtract 7 from their previous answer and then enter the new answer until the programme stopped after 2 minutes. Total number of subtractions performed, correct responses, and errors were recorded.

2.2.4.10 Rapid Visual Information Processing (Attention and Vigilance)

A continuous series of digits was presented in the centre of the screen and participants were instructed to press the spacebar whenever they detected sequences of any three consecutive odd digits, or three consecutive even digits. For example, 2, 6, 8 and 8, 4, 2 are examples of even sequences and 1, 3, 5 and 9, 7, 3 are examples of odd sequences. Participants were instructed to respond as quickly and as accurately as possible. Data was recorded over the 5 minutes duration of the task for the percentage of correct responses, the correct response RT, and the number of false alarms.

2.2.4.11 Card Sorting (Executive Function)

A version of the Wisconsin Card Sorting Task (Toone, Okocha, Sivakumar, & Syed, 2000) was presented. Participants were given limited information about how to proceed and were told that they must match each card that appears at the bottom of the screen by colour, shape and number of shapes to one of the four piles (numbered 1, 2, 3, 4) in the upper part of the screen. The cards were matched using the mouse to click on the pile to which the participant thought it belonged. No instructions were given about 'how' to match the cards, but responses were stated as being correct or incorrect each time. There was no time limit on this task and measures taken were total Responses, % Correct, Overall Response RT, and Correct Response RT.

2.2.4.12 Delayed Word Recall (Episodic Memory)

Using the recall sheets provided, participants were given 90 seconds to write down as many of the fifteen words presented earlier in the current test battery that they could remember. They were instructed to drop the recall sheet on the floor behind them when they had finished, and these were collected by the researcher. Scores for correctly recalled words were manually tallied by the researcher.

2.2.4.13 Word Recognition (Episodic Memory)

The original 15 words presented earlier, plus an additional 15 distractor words, were individually and randomly presented on the screen. For each presented word, the participant was asked whether or not the word was one of the words included in the original list of words. Participants were asked to respond as quickly as possible by pressing appropriate 'yes' and 'no' keys on the keyboard. There were no time limits and the stimuli remained on screen until the participant made a response. Measures of mean RT and accuracy were recorded.

2.2.4.14 Picture Recognition

The original 15 pictures presented earlier, plus an additional 15 distractor pictures, were individually and randomly presented on the screen. For each presented picture, the participant was asked whether or not the picture was one of the pictures included in the original display of pictures. Participants were asked to respond as quickly as possible by pressing appropriate 'yes' and 'no' keys on the keyboard. There were no time limits and the stimuli remained on screen until the participant made a response. Measures of mean RT and accuracy were recorded.

2.2.4.15 Bond Lader Mood Scales

Mood was again assessed post-tasks using the COMPASS Bond Lader mood scales in which participants used the mouse to indicate the point on the scale which was indicative of how they were feeling. Bond Lader (Bond & Lader, 1974)measures were taken for how 'alert', 'calm' and 'contented' participants were feeling.

2.2.4.16 Physical and Mental State Scales

Physical and mental state were again assessed post-tasks using the COMPASS Visual Analogue Scales, following on from the Bond Lader assessments. Again, participants used the mouse to indicate the point on the scale which was indicative of how they were feeling. Physical and mental state assessments were collected for participants' levels of 'mental energy', 'concentration', 'fullness', 'physical stamina', mental fatigue', 'hunger', 'mental stamina', 'physical tiredness', 'thirst', 'mentally tired'. At the end of the post-treatment set of physical and mental state scales participants were asked to rate how 'difficult' they found the tasks.

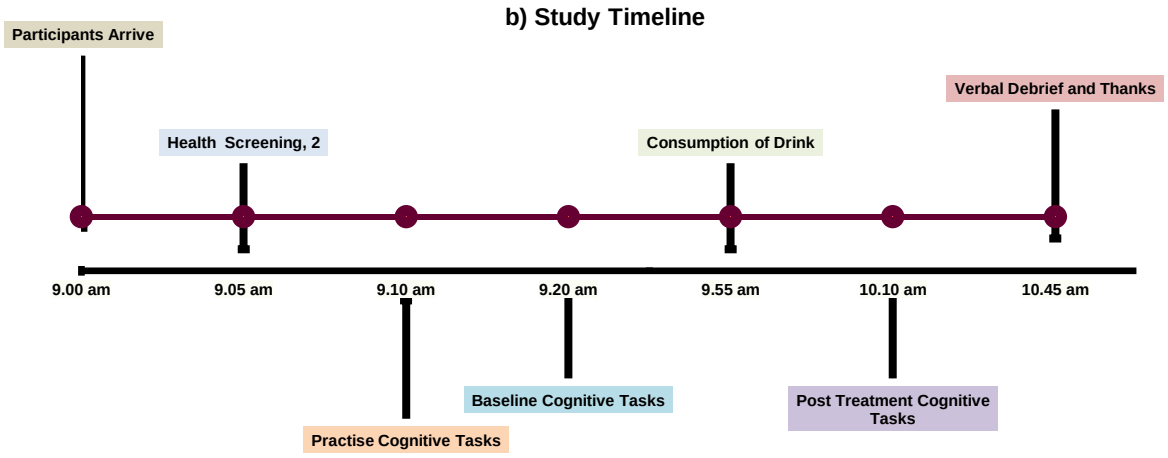
2.2.5 Procedure

Participants arrived in groups of, on average 15 per session. Sixty-five participants attended sessions which began at 9.00 am, 57 participants attended at 11.00 am and 8 participants attended at 1.00 pm. Before the session began health screening information and informed consent was sought. The researcher ensured participants were clear on what was expected of them, checked the screening forms for any allergies to the drink ingredients, checked to ensure the participants met the inclusion criteria, invited questions, and reiterated that participation was voluntary.

A practice set of tests with verbal instruction as well as task related onscreen was performed to train participants on each of the tasks that were to be used. To eliminate practice effects, sufficient practice trials were conducted to ensure that participants were familiar with the task procedures prior to data collection. As well as on-screen instruction for the tasks the researcher went through the tasks on the room projector to demonstrate. It was then ascertained whether all participants understood the procedure. Following the practice participants completed the first set of tasks in the order shown in figure 2.3 to attain a baseline measure of their performance.

All study paperwork had been numbered in advance and each participant was randomly assigned to one of the six drink conditions; drinks were numbered and coded at the preparation stage. Following the baseline assessment, participants were handed their allocated drink and were given 5 minutes to consume it; after the 5 minutes had lapsed the 10-minute absorption period began during which participants were asked to sit quietly and at rest. The post-treatment assessment was then completed to ascertain whether the drinks may have influenced cognition. The structure of the sessions can be seen in Figure 2.2 below.

Figure 2.2 Schematic of study day running order.



2.2.6 Statistics

2.2.6.1 Data Cleaning

Data was screened and cleaned prior to analysis. Where non-sensible values and missing data were found these were omitted from the analyses using listwise deletion. Datasets were checked for normal distribution and further assumptions of ANCOVA, as such linear relationships between the dependent variable and the covariate in each of the treatment conditions, homogeneity of regression slopes, and checks for, and removal of multivariate outliers.

2.2.6.2 Bond Lader Mood Scales, Physical and Mental State Scales.

For Bond Lader and Physical and Mental State scales any differences in baseline measures were primarily analysed via one-way ((6)Treatment) ANOVA. Where no significant differences were found at baseline, data was analysed via two-way mixed factorial ((4)Time x (6)Treatment) ANOVA. For significant findings ($p<0.05$) Bonferroni adjusted post hoc pairwise comparisons were conducted. The rationale for four measures being included being that participant's baseline pre-task scores could be compared, and additionally post-treatment pre-tasks and post-treatment post-tasks would give measures following treatment absorption both before and after the cognitive tasks were performed.

2.2.6.3 Cognitive Assessments

Data analysis was conducted to specifically control for any differences in baseline scores. Prior to ANCOVA one-way ((6) Treatment) ANOVAs were conducted to explore any differences in baseline scores between the treatment groups. The COMPASS cognitive tasks battery data were analysed initially using one-way ((6) Treatment) ANOVA, to assess any treatment differences at post-treatment. This was followed by one-way ((6) Treatment) ANCOVA of the data collected at post-treatment, with the data collected at baseline (pre-treatment) as the covariate. For those instances where the assumption of homogeneity of regression slopes was not violated, significant effects of treatment were further investigated with five a priori planned contrasts being made between the water and the five potentially active treatments (glucose, saccharin, aspartame, Robinsons, and lemon juice). Where there was heterogeneity of regression slopes ANCOHET have been reported, and the Maxwell and Delaney (2004) method was used to conduct the contrasts. The t-values for the planned contrasts were calculated according to Clark-Carter's formulae (2019) and compared to Bonferroni corrected critical t-values to assess significance (Clark-Carter, personal correspondence). Effect sizes for significant contrasts are calculated as Cohen's d (Clark-Carter, 2019).

2.3 Results

2.3.1 Demographic Data Analysis

See Table 2.3 below for means and SEMs of participants' age, education years, BMI and number of cigarettes smoked per day; for the three categorical variables, smokers and eyesight correction are shown as counts of 'no' or 'yes' with handedness being indicated as 'right' or 'left'

Table 2.3 Demographic information by treatment groups and sex.

Treatment Group	Sex	N	Age (years)*			Education (years)*			BMI (kg/m^2) #			Smokers*		Cigarettes Smoked Per Day *			Eyesight Correction *		Handedness *	
			Mean	±	SEM	Mean	±	SEM	Mean	±	SEM	NO	YES	Mean	±	SEM	NO	YES	Right	Left
Glucose	Females	16	21.06	±	1.01	15.06	±	0.11	26.22	±	1.82	15	1	12.50	±	0.00	13	3	14	2
	Males	6	20.33	±	0.49	15.00	±	0.26	21.86	±	1.03	6	0	.	±	.	5	1	5	1
Saccharin	Females	20	23.25	±	2.09	15.90	±	0.37	27.78	±	1.61	14	6	8.75	±	1.55	12	7	19	1
	Males	2	21.50	±	0.50	15.00	±	0.00	22.37	±	0.10	2	0	.	±	.	2	0	1	1
Aspartame	Females	22	20.68	±	0.45	15.14	±	0.07	25.50	±	0.97	18	4	6.38	±	1.52	10	12	21	1
	Males	1	27.00	±	0.00	20.00	±	0.00	30.67	±	0.00	1	0	.	±	.	0	1	1	0
RSFOC	Females	19	23.74	±	1.75	15.89	±	0.37	27.40	±	1.80	15	4	11.13	±	2.90	11	8	17	2
	Males	2	20.00	±	0.00	15.00	±	0.00	27.63	±	2.17	1	1	15.00	±	0.00	1	1	1	1
Lemon Juice	Females	19	24.11	±	1.75	15.05	±	0.25	29.19	±	1.71	14	5	9.00	±	2.10	12	7	19	0
	Males	1	20.00	±	0.00	12.00	±	0.00	27.31	±	0.00	1	0	.	±	.	0	1	1	0
Water	Females	18	24.22	±	1.59	14.83	±	0.25	25.14	±	1.35	11	7	7.36	±	1.29	7	11	15	3
	Males	4	20.00	±	0.41	15.00	±	0.00	26.10	±	2.78	3	1	10.00	±	0.00	3	1	3	1

With the exception of years in education, there were no significant differences in demographic measures between treatment groups, see Table 2.4 below for statistical justifications. Whilst there was a significant effect of treatment for years in education, there were no significant Bonferroni adjusted pairwise comparisons between treatment groups.

Table 2.4 Demographic data one-way (6)Treatment ANOVAs F values, degrees of freedom, significance levels and effect sizes are indicated.

Demographic Information	df	F	p value	R
Sex = Female	(5,124)	1.62	0.16	0.25
Sex = Male	(5,124)	1.62	0.16	0.25
Age	(5,124)	0.99	0.427	0.20
Years in Education	(5,124)	2.801	0.02	0.32
BMI	(5,124)	1.169	0.328	0.21
Smoker = No	(5,124)	1.466	0.206	0.24
Smoker = Y	(5,124)	1.466	0.206	0.24
Cigarettes Smoked Per Day	(5,28)	1.162	0.357	0.45
Handedness = Right	(5,124)	1.085	0.372	0.21
Handedness = Left	(5,124)	1.085	0.372	0.21
Eyesight correction = No	(5,124)	1.818	0.07	0.26
Eyesight correction = Yes	(5,124)	1.818	0.07	0.26

2.3.2 Bond Lader Mood Scales

There were no significant differences in baseline scores across the treatment groups for any of the Bond Lader measures. See Table 2.5 below for means and SEMs of the primary two-way ANOVA, significant effects are indicated.

Table 2.5 Bond Lader mood scales. Means, SEMs and any significant effects of treatment are indicated.

Outcome	Treatment	N=	Baseline Pre-Tasks			Baseline Post-Tasks			Post-Treatment Pre-Tasks			Post-Treatment Post_Tasks			Significant Effects of Treatment
			Means	±	SEM	Means	±	SEM	Means	±	SEM	Means	±	SEM	
Bond Lader Alert	Glucose	130	51.25	±	2.98	44.80	±	2.61	57.30	±	2.65	46.90	±	2.98	–
	Saccharin	130	54.93	±	2.27	50.60	±	2.73	58.56	±	2.64	51.06	±	3.07	
	Aspartame	130	55.61	±	2.27	52.27	±	2.93	61.92	±	2.82	54.21	±	2.59	
	Robinsons	130	50.79	±	2.78	46.22	±	2.79	55.21	±	2.27	47.58	±	2.44	
	Lemon	130	50.39	±	2.96	45.90	±	2.25	54.98	±	2.88	47.93	±	2.82	
	Water	130	50.00	±	2.73	44.27	±	2.91	53.25	±	2.02	45.79	±	2.63	
Bond Lader Calm	Glucose	130	57.95	±	2.53	58.14	±	2.25	53.66	±	2.69	59.16	±	2.40	–
	Saccharin	130	56.36	±	2.34	57.20	±	2.45	53.98	±	1.87	61.77	±	2.25	
	Aspartame	130	57.02	±	2.34	55.04	±	2.54	55.24	±	2.61	56.32	±	3.26	
	Robinsons	130	50.60	±	2.27	53.67	±	2.34	53.64	±	1.76	55.43	±	1.94	
	Lemon	130	55.65	±	2.09	52.00	±	2.20	54.73	±	2.61	54.35	±	2.82	
	Water	130	58.16	±	2.67	57.43	±	3.06	56.59	±	2.75	58.09	±	2.74	
Bond Lader Content	Glucose	130	57.88	±	3.16	53.20	±	3.10	60.67	±	3.07	55.39	±	2.78	–
	Saccharin	130	64.48	±	2.11	60.54	±	2.50	66.43	±	2.67	61.93	±	2.79	
	Aspartame	130	59.60	±	2.50	55.23	±	2.86	62.38	±	2.82	57.06	±	3.18	
	Robinsons	130	57.14	±	3.04	54.02	±	3.06	59.15	±	2.97	55.27	±	3.34	
	Lemon	130	56.72	±	3.09	50.22	±	2.75	56.17	±	2.83	53.10	±	3.16	
	Water	130	55.24	±	2.72	51.30	±	3.10	55.85	±	2.69	52.16	±	2.75	

Two-way (Treatment (6) x Time (4)) mixed factorial ANOVAs were conducted on each of the subjective measures of 'alertness', 'contentedness', 'calmness'. None of the primary two-way time x treatment ANOVA interactions were found to be significant. There were no main effects of treatment for any of the measures. See Table 2.6 below for Bond Lader results of treatment x time ANOVAs. F values, degrees of freedom, significance levels and effect sizes are indicated.

Table 2.6 Bond Lader treatment x time ANOVAs. F values, degrees of freedom, significance levels and effect sizes are indicated

Bond Lader Mood Scales	df	F	p value	r
Alertness	(15,369)	2.77	0.997	0.05
Calmness	(15,369)	1.259	0.226	0.18
Contentedness	(15,369)	0.258	0.998	0.04

2.3.3 Physical and Mental State Scales

Prior to the main analysis, one-way ((6) Treatment) ANOVAs conducted on baseline scores found that there were no differences in baseline scores across the treatment groups for any of the physical and mental state measures.

See Table 2.7 below for means and SEMs of the primary analysis, significant main effects are indicated.

Table 2.7 VAS physical and mental state scales. Means, SEMs and significant treatment effects are indicated.

Outcome	Treatment	N=	Baseline Pre-Tasks			Baseline Post-Tasks			Post-Treatment Pre-Tasks			Post-Treatment Post_Tasks			Significant Effects of Treatment
			Means	±	SEM	Means	±	SEM	Means	±	SEM	Means	±	SEM	
Mental Energy	Glucose	22	51.59	±	2.98	54.09	±	2.61	41.00	±	3.76	42.32	±	3.47	Treatment*
	Saccharin	22	52.18	±	2.34	54.77	±	3.40	45.68	±	3.71	45.27	±	3.76	
	Aspartame	22	52.57	±	2.98	59.83	±	2.18	49.41	±	2.80	54.52	±	2.90	
	Robinsons	21	53.81	±	3.42	53.90	±	3.18	46.48	±	3.43	44.52	±	3.72	
	Lemon	20	44.75	±	3.19	56.50	±	2.92	36.25	±	3.05	44.65	±	2.99	
	Water	22	43.64	±	3.28	52.23	±	2.55	40.50	±	3.48	40.23	±	3.39	
Concentration	Glucose	22	48.95	±	3.59	54.50	±	3.93	42.82	±	3.15	44.82	±	2.88	-
	Saccharin	22	56.32	±	2.63	52.86	±	3.49	46.18	±	3.23	44.73	±	3.90	
	Aspartame	22	55.00	±	2.69	60.43	±	2.96	52.82	±	4.18	53.90	±	3.05	
	Robinsons	21	51.14	±	3.82	54.95	±	3.82	44.76	±	3.91	44.29	±	3.97	
	Lemon	20	49.50	±	3.93	50.75	±	3.68	41.65	±	3.63	45.70	±	4.00	
	Water	22	49.73	±	3.09	50.95	±	2.92	39.82	±	3.75	41.18	±	3.24	
Fullness	Glucose	22	38.64	±	2.87	44.32	±	3.44	35.00	±	2.33	39.77	±	2.57	-
	Saccharin	22	49.23	±	3.35	53.68	±	2.84	44.14	±	3.26	50.09	±	3.02	
	Aspartame	22	42.48	±	2.25	46.43	±	3.20	39.00	±	3.13	40.86	±	3.29	
	Robinsons	21	47.38	±	3.84	37.24	±	3.50	36.95	±	3.66	37.57	±	4.67	
	Lemon	20	46.00	±	3.93	46.85	±	3.32	40.60	±	4.11	46.80	±	3.79	
	Water	22	41.64	±	3.45	45.68	±	3.43	38.91	±	3.44	39.59	±	3.95	
Physical Stamina	Glucose	22	51.14	±	3.11	55.59	±	4.04	48.00	±	3.88	46.82	±	3.71	-
	Saccharin	22	49.55	±	3.24	53.32	±	3.24	45.09	±	3.32	47.68	±	3.52	
	Aspartame	22	45.52	±	2.95	52.48	±	3.17	45.77	±	3.46	53.62	±	3.36	
	Robinsons	21	47.90	±	4.03	54.76	±	3.51	50.14	±	3.64	47.52	±	3.62	
	Lemon	20	41.30	±	3.45	45.80	±	2.94	36.40	±	2.82	38.30	±	2.97	
	Water	22	41.73	±	2.92	47.45	±	2.98	41.55	±	3.74	43.95	±	3.93	
Mental Fatigue	Glucose	22	52.77	±	3.48	43.41	±	3.13	55.73	±	3.38	53.27	±	2.75	-
	Saccharin	22	46.68	±	3.10	44.77	±	3.42	53.55	±	3.34	50.73	±	3.98	
	Aspartame	22	50.13	±	2.93	45.83	±	2.96	54.59	±	3.00	49.29	±	3.86	
	Robinsons	21	51.52	±	3.49	43.90	±	3.43	57.05	±	3.15	52.71	±	3.74	
	Lemon	20	53.60	±	4.26	52.60	±	3.69	60.40	±	3.11	59.30	±	4.17	
	Water	22	51.00	±	2.99	50.64	±	3.06	53.68	±	3.76	56.64	±	3.69	
Hunger	Glucose	22	50.64	±	3.96	48.86	±	3.51	52.64	±	3.57	49.36	±	4.24	-
	Saccharin	22	48.68	±	4.95	47.55	±	4.06	52.00	±	5.00	47.95	±	4.46	
	Aspartame	22	58.52	±	2.66	53.00	±	4.32	59.27	±	3.11	59.14	±	3.96	
	Robinsons	21	54.14	±	4.31	60.38	±	4.41	61.76	±	4.51	66.14	±	4.99	
	Lemon	20	51.00	±	3.96	51.65	±	3.47	57.60	±	3.94	56.55	±	3.95	
	Water	22	46.50	±	4.71	49.68	±	4.19	53.59	±	5.24	55.82	±	5.87	
Mental Stamina	Glucose	22	49.09	±	3.57	53.32	±	3.10	44.77	±	3.45	48.73	±	2.54	-
	Saccharin	22	51.50	±	2.54	55.41	±	2.83	46.82	±	3.11	47.18	±	3.34	
	Aspartame	22	52.43	±	2.46	57.96	±	2.68	50.23	±	3.37	54.95	±	2.81	
	Robinsons	21	51.52	±	2.92	53.52	±	3.13	45.19	±	3.23	50.14	±	4.18	
	Lemon	20	45.30	±	3.77	45.50	±	2.68	41.15	±	3.30	43.55	±	3.37	
	Water	22	45.64	±	3.54	50.05	±	3.02	41.32	±	3.92	39.55	±	3.46	
Physically Tired	Glucose	22	54.00	±	4.04	46.09	±	3.50	57.23	±	3.97	58.59	±	3.16	-
	Saccharin	22	49.50	±	3.37	44.86	±	3.18	56.73	±	3.36	55.45	±	2.98	
	Aspartame	22	50.17	±	3.31	42.43	±	3.30	53.27	±	3.19	45.14	±	3.97	
	Robinsons	21	50.33	±	3.71	47.81	±	3.60	50.95	±	4.47	51.67	±	4.10	
	Lemon	20	55.05	±	4.45	48.25	±	3.81	61.95	±	3.14	57.55	±	3.79	
	Water	22	53.68	±	3.72	54.55	±	3.30	59.09	±	4.08	61.09	±	3.49	
Thirst	Glucose	22	53.18	±	3.42	46.32	±	4.11	56.82	±	3.70	46.68	±	4.44	-
	Saccharin	22	60.18	±	4.15	45.41	±	4.15	65.27	±	4.01	48.41	±	4.79	
	Aspartame	22	56.26	±	3.64	36.61	±	4.17	57.77	±	3.95	45.43	±	4.64	
	Robinsons	21	57.90	±	4.09	48.14	±	4.41	61.90	±	4.35	52.81	±	4.77	
	Lemon	20	61.95	±	4.50	43.45	±	4.20	59.45	±	3.85	51.30	±	4.32	
	Water	22	57.73	±	4.19	35.86	±	3.79	59.77	±	4.32	42.77	±	4.82	
Mentally Tired	Glucose	22	55.32	±	3.55	44.27	±	3.23	59.18	±	3.52	58.68	±	3.26	-
	Saccharin	22	53.27	±	3.78	43.09	±	2.92	56.55	±	3.31	51.27	±	3.77	
	Aspartame	22	50.61	±	2.91	45.04	±	3.16	52.50	±	3.09	48.86	±	4.06	
	Robinsons	21	51.29	±	3.83	45.90	±	3.59	57.00	±	3.64	55.52	±	3.80	
	Lemon	20	55.35	±	4.30	54.25	±	3.54	63.65	±	3.20	58.05	±	3.93	
	Water	22	54.77	±	3.99	54.14	±	3.15	60.50	±	3.59	63.27	±	3.41	
Perceived Task Difficulty (Measures taken at end of test phases only)	Glucose	22	n/a	±	n/a	42.36	±	3.37	n/a	±	n/a	43.41	±	3.19	-
	Saccharin	22	n/a	±	n/a	38.59	±	3.41	n/a	±	n/a	40.09	±	3.75	
	Aspartame	22	n/a	±	n/a	41.09	±	2.59	n/a	±	n/a	39.76	±	3.21	
	Robinsons	21	n/a	±	n/a	46.24	±	4.40	n/a	±	n/a	38.29	±	3.95	
	Lemon	20	n/a	±	n/a	50.60	±	4.14	n/a	±	n/a	42.25	±	4.51	
	Water	22	n/a	±	n/a	43.14	±	3.64	n/a	±	n/a	41.05	±	4.28	

Two-way mixed factorial (Treatment (6) x Time (4)) ANOVAs were conducted on each of the subjective measures of 'mental energy', 'concentration', 'fullness', 'physical stamina', 'mental fatigue', 'hunger', 'mental stamina', 'physical tiredness', 'thirst' and 'mental tiredness'. None of the primary two-way interactions were found to be significant, see Table 2.8 below for statistical justifications.

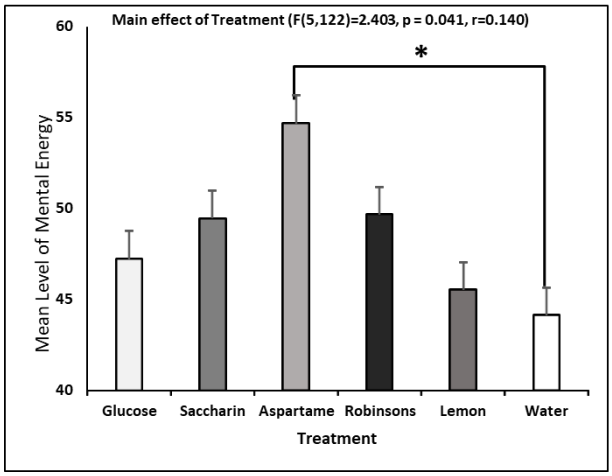
Table 2.8 Physical and Mental States. Treatment x time ANOVAs. F values, degrees of freedom, significance levels and effect sizes are indicated

Physical and Mental States	df	F	p value	r
Mental Energy	(15,366)	1.230	0.246	0.17
Concentration	(15,366)	0.478	0.951	0.09
Fullness	(15,366)	1.383	0.152	0.13
Physical Stamina	(15,366)	0.827	0.648	0.10
Mental Fatigue	(15,366)	0.685	0.799	0.10
Hunger	(15,366)	1.090	0.364	0.10
Mental Stamina	(15,366)	0.641	0.841	0.09
Physical Tiredness	(15,366)	1.224	0.250	0.12
Thirst	(15,366)	1.171	0.292	0.11
Mental Tiredness	(15,366)	1.152	0.308	0.12

2.3.3.1 Mental Energy

For mental energy, there was a main effect of treatment ($F(5,122)=2.403$, $p = 0.041$, $r=0.14$) with pairwise comparison of aspartame and water ($t(122) = 3.113$, $p = .035$) revealing significantly higher levels of mental energy in the aspartame treatment compared to the water treatment, see Table 2.7 above for means and SEMs and Figure 2.3 below..

Figure 2.3 Mental energy, main effect of Treatment. Bars show standard error. See figure key for significance levels. (p<.05)*.**



2.3.4 Summary of Mood, and Mental and Physical State Results

For the mental and physical state data, mental energy was the only measure which showed a main effect of treatment, with post hoc comparisons showing that when compared to the water condition, the aspartame group had higher levels of mental energy.

2.3.5 Cognitive Assessments

2.3.5.1 Immediate -Word Recall (Episodic memory)

Prior to the main analysis, a one-way ANOVA conducted on baseline scores found that there were no differences in baseline scores across the treatment groups (p = .682).

See Table 2.9 below for means, SEM and main effects, any significant treatment effects are indicated.

Table 2.9 Immediate Word Recall, percentages of correct responses. Means and SEMs for baseline and post-treatment scores. Significant effects of treatment are indicated.

Outcome	Treatment	N=	Baseline			Post-Treatment			Significant Effects
			Means	±	SEM	Means	±	SEM	
Immediate Word Recall Correctly Recalled Words	Glucose	22	52.42	±	3.41	43.33	±	3.50	–
	Saccharin	22	46.06	±	2.63	42.42	±	2.65	
	Aspartame	22	50.00	±	3.64	47.27	±	3.67	
	Robinsons	21	52.06	±	3.70	49.84	±	3.55	
	Lemon	20	52.33	±	2.99	45.00	±	3.68	
	Water	22	47.88	±	3.74	41.52	±	3.72	

A one-way ANCOVA was conducted to assess the impact of treatments on post-treatment scores for the percentage correct responses for immediate word recall. After controlling for baseline scores, there was a non-significant difference in post-treatment scores between the treatment groups ($F(5,122) = 0.0719$, $p = .61$, $r = 0.154$), see Table 2.9 above for mean and SEMs.

2.3.5.2 Delayed Word Recall (Episodic memory)

There were no differences in baseline scores across the treatment groups ($p = .789$).

For delayed word recall means and SEMs see Table 2.10 below, any significant treatment effects are indicated.

Table 2.10 Delayed Word Recall percentages of correct responses. Means and SEMs for baseline and post-treatment scores. Significant effects of treatment are indicated.

Outcome	Treatment	N=	Baseline			Post-Treatment			Significant Effects
			Means	±	SEM	Means	±	SEM	
Delayed Word Recall Percentages of Correctly Recalled Words	Glucose	22	32.12	±	4.20	25.15	±	4.25	–
	Saccharin	22	31.21	±	2.82	23.33	±	3.03	
	Aspartame	22	36.67	±	4.22	34.85	±	4.27	
	Robinsons	21	38.10	±	4.58	32.38	±	4.72	
	Lemon	20	36.67	±	4.20	26.67	±	4.33	
	Water	22	36.36	±	4.16	30.30	±	4.13	

After controlling for baseline scores, there were no significant differences in post-treatment scores between the treatment groups ($F(5,122) = 0.902$, $p = .482$, $r = 0.157$), see Table 2.10 above for means, SEMs.

2.3.5.2.1 Summary of Word Recall (Immediate and delayed) Results

After controlling for baseline scores there were no treatment differences in the percentages of correctly recalled words at post-treatment. This was found to be the case for both immediate and delayed recall.

2.3.5.3 Stroop Test (Attention/Response Inhibition)

See Table 2.11below for Stroop task means and SEMs, any significant treatment effects are indicated.

Table 2.11 Stroop task. Means and SEMs for baseline and post-treatment scores. Significant effects of treatments are indicated (p<.05; **p<.005)***

Outcome	Treatment	N=	Baseline			Post-Treatment			Significant Effects
			Means	±	SEM	Means	±	SEM	
% Correct Responses	Glucose	21	99.43	±	0.24	99.33	±	0.32	–
	Saccharin	21	99.05	±	0.51	98.67	±	0.42	
	Aspartame	23	98.87	±	0.30	99.39	±	0.29	
	Robinsons	20	99.50	±	0.20	99.30	±	0.22	
	Lemon	20	99.30	±	0.22	99.20	±	0.37	
	Water	22	99.55	±	0.18	99.27	±	0.38	
% Correct Congruent Responses	Glucose	22	99.06	±	0.67	99.50	±	0.35	–
	Saccharin	22	100.00	±	0.00	99.20	±	0.46	
	Aspartame	23	99.03	±	0.46	99.07	±	0.52	
	Robinsons	21	99.72	±	0.28	99.06	±	0.54	
	Lemon	20	99.30	±	0.48	99.19	±	0.60	
	Water	22	99.70	±	0.30	99.26	±	0.55	
% Correct Incongruent Responses	Glucose	21	99.15	±	0.37	99.22	±	0.39	–
	Saccharin	20	99.59	±	0.23	99.42	±	0.27	
	Aspartame	23	99.02	±	0.38	99.55	±	0.25	
	Robinsons	21	99.33	±	0.27	99.10	±	0.32	
	Lemon	20	99.29	±	0.28	99.28	±	0.34	
	Water	21	99.32	±	0.27	99.28	±	0.36	
Correct Overall Response Reaction Time	Glucose	20	905.46	±	32.72	871.99	±	31.67	Treatment**
	Saccharin	22	985.84	±	41.04	944.90	±	45.01	
	Aspartame	23	864.35	±	30.59	821.61	±	18.35	
	Robinsons	21	903.73	±	22.06	881.88	±	20.84	
	Lemon	19	953.95	±	42.37	844.33	±	29.49	
	Water	22	910.52	±	28.46	879.12	±	22.78	
Correct Congruent Responses Reaction Time	Glucose	22	922.98	±	41.31	889.93	±	33.39	–
	Saccharin	20	917.36	±	25.50	883.60	±	32.64	
	Aspartame	23	843.58	±	32.35	817.27	±	18.47	
	Robinsons	21	892.08	±	28.21	847.23	±	22.67	
	Lemon	19	908.98	±	39.65	826.40	±	31.67	
	Water	22	877.79	±	26.54	858.94	±	24.88	
Correct Incongruent Responses Reaction Time	Glucose	22	925.50	±	31.52	909.19	±	37.24	–
	Saccharin	21	1004.84	±	52.50	964.99	±	58.28	
	Aspartame	23	861.67	±	27.66	819.77	±	18.48	
	Robinsons	21	902.46	±	19.67	887.13	±	19.76	
	Lemon	20	996.38	±	50.30	879.01	±	31.09	
	Water	22	966.58	±	35.51	910.62	±	30.04	

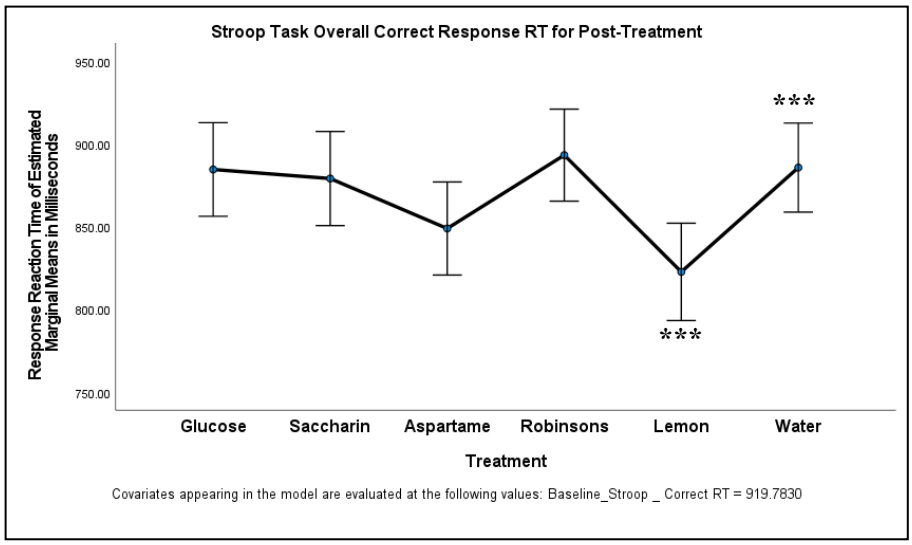
No significant baseline differences were found between the treatment groups (p = .521). For the percentage of correct responses for the Stroop task, there was significant heterogeneity of regression slopes (F(5,115) = 0.3471, p = .006, r= 0.005). After controlling for baseline scores, there was a significant difference in the percentage of correct responses at post-treatment between the treatment groups (F(5,115) = 3.486, p = .006, r= 0.005). However, planned contrasts conducted to account for heterogeneity (Maxwell and Delaney,2004) did not reveal any significant comparisons. see Table 2.11 above for means, SEMs.

There were no significant baseline differences in the percentages of correct congruent Stroop judgements between the treatment groups (p = .483). After controlling for baseline scores, there was no significant difference in the percentage of correct congruent responses at post-treatment between the treatment groups (F(5,123) = 0.096, p = .93, r= 0.062), see Table 2.11 above for means, SEMs.

No significant baseline differences for percentage of correct incongruent responses between the treatment groups were found (p = .859). After controlling for baseline scores, there was a non-significant difference in the percentage of correct incongruent responses for the Stroop task at post-treatment between the treatment groups (F(5,121) = 0.456, p = .81, r= 0.131), see Table 2.11 above for means, SEMs.

For Stroop correct overall response RT, no significant baseline differences were identified. ANCOVA identified that there was significant heterogeneity of regression slopes (F(5,115) = 4.655, <.001, r= 0.198). After controlling for baseline scores, there was a significant difference in response RTs at post-treatment between the treatment groups (F(5,115) = 3.701, p = .004, r= 0.1767). A set of planned contrasts conducted to account for heterogeneity (Maxwell and Delaney, 2004) revealed a significant comparison between the water control (Mean 885.73; SEM 13.60) and lemon juice (Mean 822.604; SEM 14.86) treatments (observed t(123) = 3.168, the Bonferroni corrected critical t = 2.617, d = 0.39), see Figure 2.4 below and Table 2.11 above for means and SEMs.

Figure 2.4 Stroop Task, Overall Correct Response RTs. ANCOVA estimated marginal means of post-treatment whilst controlling for the covariate. Bars show standard error. (*p<.001)**



No significant baseline differences were found for correct congruent response RT. ANCOVA identified that there was significant heterogeneity of regression slopes (F(5,115) = 3.228, p = .009, r= 0.201). After controlling for baseline scores, there was a significant difference in the response RTs at post-treatment between the treatment groups (F(5,115) = 2.892, p = .017, r= 0.194). However, planned contrasts conducted to account for heterogeneity (Maxwell and Delaney,2004) did not reveal any significant comparisons. See Table 2.11 above for means and SEMs.

No significant baseline differences were found for correct incongruent response RT.ANCOVA identified that there was significant heterogeneity of regression slopes (F(5,115) = 6.357, p<.001, r= 0.245). After controlling for baseline scores, there was a significant difference in the response RTs at post-treatment between the treatment groups (F(5,115) = 4.69, p<.001, r= 0.210). However, planned contrasts conducted to account for heterogeneity (Maxwell and Delaney,2004) did not reveal any significant comparisons. See Table 2.11 above for means and SEMs.

2.3.5.3.1 Stroop Task Summary of Results

For Stroop overall response RTs and for overall correct response RTs faster responses were made in the lemon juice condition compared to the water control. In terms of the secondary aim of this chapter, glucose had no influence on the outcomes of any of the components of the Stroop task.

2.3.5.4 Simple Reaction Time (Psychomotor performance/Attention)

See Table 2.12 below for the simple RT task means and SEMs, any significant treatment effects are indicated. There were no significant baseline differences between the treatment groups (p = .262).

Table 2.12 Simple reaction time task. Means and SEMs for baseline and post-treatment scores. Significant effects of treatment are indicated.

Outcome	Treatment	N=	Baseline			Post-Treatment			Significant Effects
			Means	±	SEM	Means	±	SEM	
Overall Reaction Time	Glucose	20	342.07	±	8.99	356.60	±	10.20	Treatment*
	Saccharin	22	357.25	±	10.62	381.39	±	11.47	
	Aspartame	23	341.24	±	8.27	344.70	±	6.82	
	Robinsons	21	342.88	±	9.04	370.90	±	15.16	
	Lemon	19	334.66	±	7.57	342.65	±	8.68	
	Water	22	363.25	±	11.45	372.27	±	13.05	

For the simple reaction time task, the one-way ANCOVA identified significant heterogeneity of regression slopes ($F(5,115) = 2.589$, $p = .029$, $r = 0.203$). After controlling for baseline scores, there was a significant difference in simple RTs at post-treatment between the treatment groups ($F(5,115) = 2.38$, $p = .043$, $r = 0.194$). However, planned contrasts conducted to account for heterogeneity (Maxwell and Delaney,2004) did not reveal any significant comparisons. see Table 2.12 above for means and SEMs.

2.3.5.5 Choice Reaction Time (Psychomotor performance/Attention)

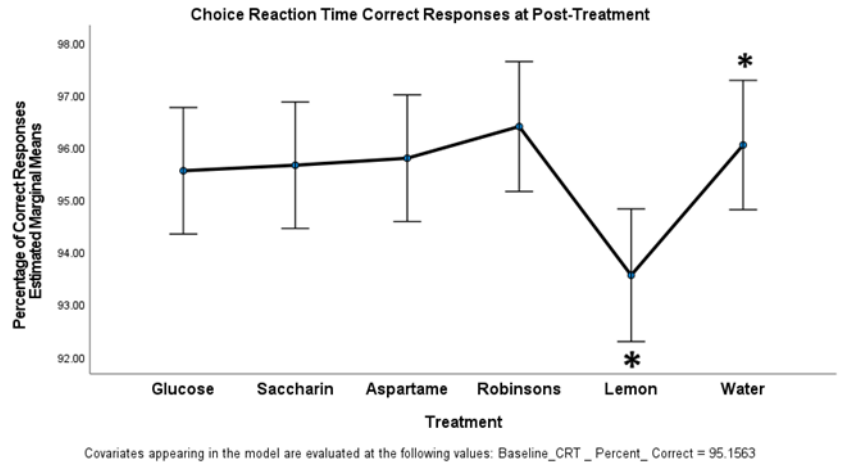
For Choice RT data means and SEMs, see Table 2.13 below, any significant treatment effects are indicated.

Table 2.13 Choice reaction time task. Means, SEMs and significant effects of treatment are indicated *(*p<0.05).*

Outcome	Treatment	N=	Baseline			Post-Treatment			Significant Effects
			Means	±	SEM	Means	±	SEM	
% Correct Responses	Glucose	22	94.82	±	0.54	95.36	±	0.75	Treatment *
	Saccharin	22	95.45	±	0.75	95.82	±	0.87	
	Aspartame	22	94.55	±	0.92	95.45	±	0.80	
	Robinsons	21	96.00	±	0.60	96.86	±	0.47	
	Lemon	20	94.70	±	1.05	93.30	±	0.92	
	Water	21	95.43	±	0.69	96.19	±	0.57	
Overall Response Reaction Time	Glucose	22	467.22	±	12.79	481.27	±	18.40	-
	Saccharin	22	498.14	±	20.09	497.08	±	17.84	
	Aspartame	23	447.97	±	10.47	443.26	±	11.14	
	Robinsons	21	463.54	±	10.65	479.39	±	15.73	
	Lemon	20	456.62	±	9.56	460.18	±	12.14	
	Water	22	469.16	±	12.92	486.71	±	16.91	
Correct Response Reaction Time	Glucose	22	471.93	±	12.83	484.52	±	18.33	-
	Saccharin	22	511.31	±	20.88	515.93	±	23.17	
	Aspartame	23	451.12	±	10.75	446.84	±	11.86	
	Robinsons	21	467.24	±	10.87	482.14	±	15.95	
	Lemon	20	460.52	±	9.62	465.28	±	12.42	
	Water	22	472.28	±	13.11	490.85	±	17.32	

For percentages of correct choice reaction time responses, no significant baseline differences were found. ANCOVA revealed that the assumption of homogeneity of regression slopes was met (F(5,116) = 1.353, p = .247 r= 0.184). After controlling for baseline scores, the full factorial model revealed a significant difference in the percentages of correct choices made at post-treatment between the treatment groups (F(5,121) = 2.459, p = .037, r= 0.25). A set of planned contrasts identified a significant comparison between the water control (Mean 96.04; SEM 0.63) and lemon juice (Mean 93.55; SEM 0.64) treatments (observed t(123) = 2.779, the Bonferroni corrected critical t = 2.616, d = 0.37), see Figure 2.5 below and Table 2.13 above for means and SEMs.

Figure 2.5 Choice Reaction Time percentages of correct responses. ANCOVA estimated marginal means of post-treatment whilst controlling for the covariate. Bars show standard error. (p<.01)***



No significant baseline differences were found for overall response RTs. After controlling for baseline scores, there was a non-significant difference in overall response RTs at post-treatment between the treatment groups (F(5,123) = 0.838, p = .53, r= 0.098), see Table 2.13 above for means and SEMs.

No significant baseline differences were found for correct response RTs,. However, after controlling for baseline scores, there was a non-significant difference in correct response RTs at post-treatment between the treatment groups (F(5,123) = 0.753, p = .59, r= 0.096), see Table 2.13 above for means and SEMs.

2.3.5.5.1 Summary of Simple Reaction Time and Choice Reaction Time Results

For the choice reaction time task, significantly lower percentages of correct responses were made in the lemon juice condition compared to the water control. In terms of the secondary aim of this chapter, glucose had no influence on the outcomes of any of the components of the SRT and CRT tasks.

2.3.5.6 Serial 7s Subtractions (Working memory/Executive function)

For Serial 7s mean and SEMs see Table 2.14 below, any significant treatment effects are indicated.

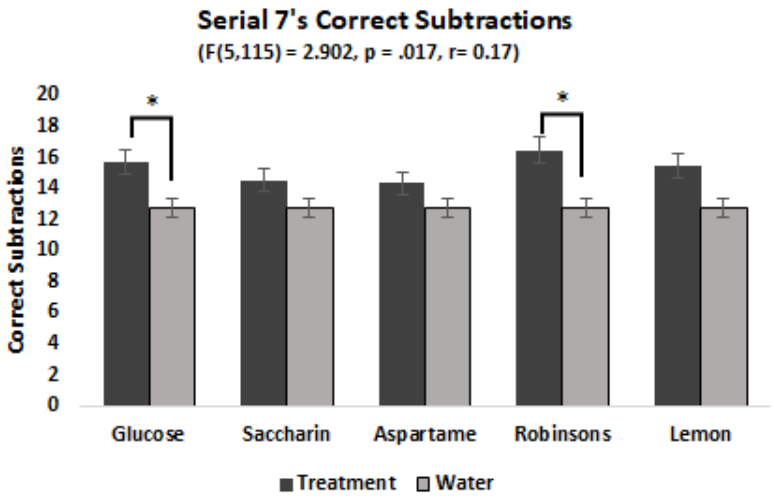
Table 2.14 Serial 7s subtraction task. Means, SEMs and significant effects are indicated (*p<0.05).

Outcome	Treatment	N=	Baseline			Post-Treatment			Significant Effects
			Means	±	SEM	Means	±	SEM	
Total Number of Subtractions	Glucose	22	15.57	±	1.51	18.10	±	1.55	–
	Saccharin	22	14.73	±	1.44	16.00	±	1.49	
	Aspartame	23	16.22	±	1.40	17.43	±	1.43	
	Robinsons	21	20.05	±	2.13	21.95	±	2.30	
	Lemon	20	17.65	±	1.39	18.25	±	1.40	
	Water	22	17.77	±	1.21	17.36	±	1.09	
Number of Correct Responses	Glucose	20	12.80	±	1.58	14.80	±	1.48	Treatment *
	Saccharin	20	12.25	±	1.37	13.15	±	1.50	
	Aspartame	22	12.82	±	1.54	13.45	±	1.44	
	Robinsons	18	16.17	±	2.21	18.50	±	2.39	
	Lemon	20	14.10	±	1.62	15.70	±	1.58	
	Water	22	15.05	±	1.29	13.77	±	1.16	

No significant baseline differences were found for the total number of Serial 7s subtractions performed. After controlling for baseline scores there were no significant effects of treatment on post-treatment scores (F(5,122) = 1.958, p = .09, r= 0.125). See Table 2.14 above for means and SEMs.

No significant baseline differences were found for the number of correct responses of Serial 7s subtractions performed. After controlling for baseline scores, the full factorial model revealed a significant difference in the percentages of correct subtractions made at post-treatment between the treatment groups (F(5,115) = 2.902, p = .017, r= 0.17). A set of planned contrasts identified a significant comparison between the water control (Mean 12.71; SEM 0.75) and both glucose (Mean 15.70; SEM 0.78) (observed t(115) = 2.755, d = 0.36) and RSFOC (Mean 16.46; SEM 0.83) (observed t(115) = 3.369, d = 0.41). The Bonferroni corrected critical t = 2.619 for both significant contrasts. See Figure 2.6 below and Table 2.13 above for means and SEMs.

Figure 2.6 Serial 7's Correct Subtractions. Planned contrasts from ANCOVA treatment effects. See figure key for significance levels *(*p < .05)* Bars show standard error.



2.3.5.6.1 Summary of Serial 7s Subtraction Results

There were no effects of treatment on the overall total number of subtractions performed. Performance on the total number of correct subtractions made were significantly higher in the glucose and RSFOC conditions compared to the water control. In terms of the secondary aim of this study, glucose appears to be enhancing cognitive domains relative to working memory and/or executive function. The influence of RSFOC was unexpected.

2.3.5.7 Rapid Visual Information Processing (Attention & Vigilance)

For RVIP mean and SEMs see Table 2.15 below, any significant treatment effects are indicated.

Table 2.15 Rapid Visual Information Processing task. Means and SEMs, significant effects are indicated.

Outcome	Treatment	N=	Baseline			Post-Treatment			Significant Effects
			Means	±	SEM	Means	±	SEM	
% Correct Responses	Glucose	22	42.80	±	4.46	43.18	±	4.11	–
	Saccharin	22	36.74	±	4.15	39.58	±	4.52	
	Aspartame	22	38.26	±	4.90	30.49	±	4.77	
	Robinsons	21	42.26	±	3.90	43.85	±	4.56	
	Lemon	19	47.15	±	5.71	41.23	±	4.67	
	Water	20	47.29	±	4.31	44.79	±	6.06	
Correct Response Reaction Time	Glucose	21	527.95	±	12.72	527.52	±	16.67	–
	Saccharin	22	542.04	±	10.78	528.88	±	15.59	
	Aspartame	23	550.28	±	15.56	529.49	±	14.71	
	Robinsons	21	517.09	±	13.04	476.46	±	14.29	
	Lemon	20	543.05	±	17.36	535.90	±	15.03	
	Water	21	523.91	±	11.32	494.34	±	14.43	
False Alarms	Glucose	21	1.73	±	0.37	1.41	±	0.35	–
	Saccharin	22	1.55	±	0.38	1.41	±	0.31	
	Aspartame	23	1.35	±	0.32	1.35	±	0.18	
	Robinsons	21	0.95	±	0.21	1.29	±	0.25	
	Lemon	20	1.75	±	0.31	1.30	±	0.27	
	Water	21	1.82	±	0.25	1.91	±	0.41	

For percentages of 'correct' RVIP responses no significant baseline differences were found. After controlling for baseline scores there were no significant effects of treatment on post-treatment scores ($F(5,119) = 1.616$, $p = .161$, $r = 0.173$). See Table 2.15 above for means and SEMs.

For correct RVIP response RTs, no significant baseline differences were). After controlling for baseline scores there were no significant effects of treatment on post-treatment scores ($F(5,120) = 1.994$, $p = .084$, $r = 0.265$). See Table 2.15 above for means and SEMs.

For RVIP 'false alarm' responses, no significant baseline differences were found. After controlling for baseline scores there were no significant effects of treatment on post-treatment scores ($F(5,123) = 0.467$, $p = .800$, $r = 1.436$). See Table 2.15 above for means and SEMs.

2.3.5.7.1 Summary of Rapid Visual Information Processing Results

There were no effects of any of the treatments on RVIP processing. In terms of the secondary aim of this study, glucose ingestion had no impact on the domains of attention and vigilance.

2.3.5.8 Card Sorting (Executive Function)

. For the card sorting task means and SEMs see Table 2.16 below, any significant treatment effects are indicated.

Table 2.16 Card Sorting task. Means, SEMs and significant effects are indicated.

Outcome	Treatment	N=	Baseline			Post-Treatment			Significant Effects
			Means	±	SEM	Means	±	SEM	
Total Number of Responses Made	Glucose	22	100.55	±	3.41	95.91	±	3.16	–
	Saccharin	22	88.18	±	3.13	83.95	±	2.97	
	Aspartame	23	98.52	±	4.63	89.57	±	3.74	
	Robinsons	21	98.67	±	3.94	89.95	±	3.37	
	Lemon	20	93.70	±	4.10	87.85	±	3.43	
	Water	22	103.09	±	4.06	93.59	±	4.58	
% Correct Response	Glucose	22	80.82	±	1.40	84.62	±	0.82	–
	Saccharin	22	82.45	±	1.16	85.59	±	1.24	
	Aspartame	23	78.85	±	2.53	83.25	±	2.06	
	Robinsons	21	79.93	±	1.56	83.88	±	1.77	
	Lemon	20	80.29	±	1.51	85.80	±	0.66	
	Water	22	78.73	±	1.78	82.39	±	1.88	
Overall Response Reaction Time	Glucose	22	1372.59	±	57.92	1204.68	±	44.63	–
	Saccharin	21	1333.95	±	60.30	1204.67	±	52.81	
	Aspartame	23	1223.26	±	39.52	1102.70	±	34.91	
	Robinsons	20	1236.15	±	40.72	1133.60	±	33.39	
	Lemon	20	1275.10	±	73.67	1052.90	±	37.14	
	Water	22	1312.18	±	59.10	1162.55	±	46.77	
Correct Response Reaction Time Average	Glucose	22	1322.77	±	54.04	1183.09	±	43.97	–
	Saccharin	21	1293.48	±	56.96	1160.67	±	44.50	
	Aspartame	23	1183.57	±	35.69	1049.52	±	24.41	
	Robinsons	21	1225.86	±	47.74	1135.95	±	38.58	
	Lemon	20	1217.15	±	61.48	1044.50	±	36.85	
	Water	22	1270.59	±	53.75	1147.45	±	44.67	

No significant baseline differences were found for the total number of card sort responses performed. After controlling for baseline scores there were no significant effects of treatment on post-treatment scores ($F(5,123) = 0.593$, $p = .705$, $r = 0.14$). See Table 2.16 above for means and SEMs.

No significant baseline differences were found for percentage of correct responses. After controlling for baseline scores there were no significant effects of treatment on post-treatment scores ($F(5,123) = 0.444$, $p = .82$, $r = 0.11$). See Table 2.16 above for means and SEMs. For overall RTs for responses, no significant baseline differences were found. After controlling for baseline scores there were no significant effects of treatment on post-treatment scores ($F(5,116) = 2.09$, $p = .08$, $r = 0.17$). See Table 2.16 above for means and SEMs.

No significant baseline differences were found for correct response RTs. After controlling for baseline scores there were no significant effects of treatment on post-treatment scores ($F(5,117) = 1.477$, $p = .20$, $r = 0.16$). See Table 2.16 above for means and SEMs.

2.3.5.8.1 Summary of Card Sort Task Results

There were no effects of any of the treatments on the card sorting tasks. In terms of the secondary aim of this study, glucose ingestion had no impact on executive function.

2.3.5.9 Word Recognition (Episodic memory)

For word recognition means and SEMs see Table 2.17 below, any significant treatment effects are indicated.

Table 2.17 Word Recognition. Means and SEMs. Significant effects are indicated (p<0.005).**

Outcome	Treatment	N=	Baseline			Post-Treatment			Significant Effects
			Means	±	SEM	Means	±	SEM	
% Correct Reponses	Glucose	22	82.88	±	1.90	76.97	±	2.69	Treatment *
	Saccharin	22	79.24	±	1.74	78.64	±	2.41	
	Aspartame	22	82.12	±	2.17	79.09	±	2.41	
	Robinsons	21	82.38	±	1.94	79.37	±	2.68	
	Lemon	19	84.74	±	1.20	78.07	±	3.13	
	Water	22	81.82	±	2.43	75.91	±	2.76	
% Correct 'YES' Responses	Glucose	22	69.09	±	3.63	69.39	±	4.59	-
	Saccharin	22	76.97	±	2.76	70.91	±	4.93	
	Aspartame	22	75.46	±	3.73	66.36	±	5.45	
	Robinsons	21	74.29	±	2.96	76.19	±	3.43	
	Lemon	20	72.00	±	4.34	71.00	±	4.87	
	Water	22	78.79	±	3.27	70.00	±	3.50	
% Correct 'NO' Responses	Glucose	22	90.00	±	2.18	90.00	±	2.55	-
	Saccharin	22	82.73	±	2.69	82.73	±	3.69	
	Aspartame	22	89.70	±	2.22	86.67	±	3.45	
	Robinsons	21	90.48	±	2.37	82.86	±	3.81	
	Lemon	20	89.67	±	1.96	83.33	±	3.50	
	Water	22	94.24	±	1.66	86.67	±	3.34	
Overall Response Reaction Time	Glucose	21	985.78	±	45.18	939.85	±	43.43	-
	Saccharin	22	1073.96	±	53.72	985.81	±	48.82	
	Aspartame	22	869.49	±	21.73	847.57	±	29.76	
	Robinsons	21	915.43	±	37.50	861.40	±	27.67	
	Lemon	20	945.80	±	28.11	888.76	±	34.49	
	Water	21	961.37	±	46.88	935.28	±	47.97	
Correct Response Reaction Time	Glucose	21	846.09	±	25.53	911.09	±	33.25	-
	Saccharin	22	899.55	±	28.52	862.01	±	22.61	
	Aspartame	22	809.89	±	21.34	808.45	±	21.63	
	Robinsons	21	832.69	±	17.42	830.24	±	17.07	
	Lemon	20	874.24	±	28.25	817.78	±	22.39	
	Water	21	850.14	±	28.84	873.05	±	26.53	
YES' Response Reaction Time	Glucose	22	801.70	±	25.14	898.25	±	38.16	-
	Saccharin	22	867.15	±	32.69	816.55	±	20.10	
	Aspartame	22	806.81	±	20.94	806.38	±	22.50	
	Robinsons	21	820.59	±	22.65	797.44	±	14.14	
	Lemon	20	859.56	±	33.11	798.09	±	26.94	
	Water	22	834.82	±	31.63	862.14	±	32.08	
NO' Response Reaction Time	Glucose	22	910.57	±	29.68	963.62	±	42.66	-
	Saccharin	22	952.69	±	39.31	933.76	±	32.96	
	Aspartame	22	833.96	±	28.01	832.46	±	26.67	
	Robinsons	21	863.29	±	24.21	879.35	±	26.92	
	Lemon	20	910.68	±	34.54	841.81	±	30.73	
	Water	21	879.94	±	33.59	895.91	±	31.28	

No significant baseline differences for the percentage of overall correct word recognition responses were found. The primary ANCOVA identified that there was significant heterogeneity of regression slopes ($F(5,116) = 3.617$, $p = .004$, $r = 0.33$). After controlling for baseline scores, there was a

significant difference in the percentage of correct responses at post-treatment between the treatment groups (F(5,116) = 3.571, p = .005, r= 0.33). However, planned contrasts conducted to account for heterogeneity (Maxwell and Delaney,2004) did not reveal any significant comparisons. see Table 2.17 above for means, SEMs.

For percentage of correct 'YES' word recognition responses, no significant baseline differences were found. After controlling for baseline scores there were no significant effects of treatment on post-treatment scores (F(5,122) = 1.376, p = .24, r= 0.19). See Table 2.17 above for means and SEMs.

For percentage of correct 'NO' word recognition responses, there was a significant baseline difference between the treatment groups (p = .02). However, after controlling for baseline scores there were no significant effects of treatment on post-treatment scores (F(5,122) = 0.813, p = .54, r= 0.16). See Table 2.17 above for means and SEMs.

There was a significant difference between the treatment groups for overall RT for word recognition responses (p = .013). However, after controlling for baseline scores there were no significant effects of treatment on post-treatment scores (F(5,120) = 0.311, p = .91, r= 0.07). See Table 2.17 above for means and SEMs.

For YES response RT for the word recognition task, there was a significant difference between the treatment groups (p = .04). However, after controlling for baseline scores there were no significant effects of treatment on post-treatment scores (F(5,122) = 0.688, p = .65, r= 0.13). See Table 2.17 above for means and SEMs.

For NO response RT for the word recognition task, there was a significant difference between the treatment groups (p = .01). However, after controlling for baseline scores there were no significant effects of treatment on post-treatment scores (F(5,116) = 2.035, p = .08, r= 0.22). See Table 2.17 above for means and SEMs.

2.3.5.9.1 Summary of Word Recognition Results

There was an effect of treatment on post-treatment scores for the percentage of correct responses made although the post hoc planned comparisons did not reveal any significant comparisons

between the treatments and the water control. In terms of the secondary aim of this study, glucose ingestion had no impact on episodic memory for words.

2.3.5.10 Picture Recognition (Episodic Memory)

For Picture recognition means and SEMs see Table 2.18 below, any significant treatment effects are indicated.

Table 2.18 Picture Recognition. Means and SEMs. Significant effects are indicated .

Outcome	Treatment	N=	Baseline			Post-Treatment			Significant Effects
			Means	±	SEM	Means	±	SEM	
% Correct Recognitions	Glucose	22	94.39	±	1.34	86.97	±	1.90	–
	Saccharin	22	95.46	±	1.04	91.06	±	1.57	
	Aspartame	22	93.77	±	1.36	90.15	±	1.87	
	Robinsons	21	94.45	±	1.51	91.59	±	1.55	
	Lemon	20	95.84	±	1.13	91.17	±	1.95	
	Water	22	93.64	±	1.55	90.61	±	1.89	
% Correct 'YES' Recognitions	Glucose	22	91.51	±	2.64	79.39	±	2.87	Treatment *
	Saccharin	22	94.85	±	1.80	88.18	±	2.56	
	Aspartame	22	92.17	±	2.20	86.06	±	2.77	
	Robinsons	21	96.19	±	1.09	87.94	±	2.46	
	Lemon	20	96.00	±	1.90	89.67	±	2.19	
	Water	22	90.30	±	2.90	86.06	±	3.42	
% Correct 'NO' Recognitions	Glucose	22	97.27	±	0.84	94.55	±	1.62	Treatment *
	Saccharin	21	96.82	±	0.88	94.92	±	1.45	
	Aspartame	22	95.15	±	1.33	94.24	±	1.82	
	Robinsons	21	92.70	±	2.34	95.24	±	1.60	
	Lemon	20	95.67	±	1.21	92.67	±	2.26	
	Water	21	97.78	±	0.70	95.87	±	1.34	
Overall Response Reaction Time	Glucose	21	859.92	±	25.40	917.62	±	32.82	Treatment *
	Saccharin	22	909.92	±	30.04	875.15	±	23.11	
	Aspartame	22	820.38	±	22.15	819.42	±	22.75	
	Robinsons	21	841.94	±	18.76	838.39	±	17.50	
	Lemon	20	885.12	±	32.28	819.95	±	23.43	
	Water	21	852.91	±	27.83	875.50	±	27.83	
Correct Response Reaction Time	Glucose	21	846.09	±	25.53	911.09	±	33.25	Treatment *
	Saccharin	22	899.55	±	28.52	862.01	±	22.61	
	Aspartame	22	809.89	±	21.34	808.45	±	21.63	
	Robinsons	21	832.69	±	17.42	830.24	±	17.07	
	Lemon	20	874.24	±	28.25	817.78	±	22.39	
	Water	21	850.14	±	28.84	873.05	±	26.53	
YES' Response Reaction Time	Glucose	22	801.70	±	25.14	898.25	±	38.16	Treatment **
	Saccharin	22	867.15	±	32.69	816.55	±	20.10	
	Aspartame	22	806.81	±	20.94	806.38	±	22.50	
	Robinsons	21	820.59	±	22.65	797.44	±	14.14	
	Lemon	20	859.56	±	33.11	798.09	±	26.94	
	Water	22	834.82	±	31.63	862.14	±	32.08	
NO' Response Reaction Time	Glucose	22	910.57	±	29.68	963.62	±	42.66	Treatment *
	Saccharin	22	952.69	±	39.31	933.76	±	32.96	
	Aspartame	22	833.96	±	28.01	832.46	±	26.67	
	Robinsons	21	863.29	±	24.21	879.35	±	26.92	
	Lemon	20	910.68	±	34.54	841.81	±	30.73	
	Water	21	879.94	±	33.59	895.91	±	31.28	

There were no baseline differences between treatment groups on any of the picture recognition measures.

After controlling for baseline scores there were no significant effects of treatment on post-treatment scores ($F(5,122) = 1.081$, $p = .37$, $r = 0.18$). See Table 2.18 above for means and SEMs.

The primary ANCOVA identified that there was significant heterogeneity of regression slopes ($F(5,116) = 2.370$, $p = .04$, $r = 0.25$). After controlling for baseline scores, there was a significant difference in the percentage of correct responses at post-treatment between the treatment groups ($F(5,116) = 2.473$, $p = .04$, $r = 0.26$). However, planned contrasts conducted to account for heterogeneity (Maxwell and Delaney,2004) did not reveal any significant comparisons. see Table 2.18 above for means, SEMs.

The primary ANCOVA identified that there was significant heterogeneity of regression slopes ($F(5,115) = 2.500$, $p = .04$, $r = 0.304$). After controlling for baseline scores, there was a significant difference in the percentage of correct responses at post-treatment between the treatment groups ($F(5,115) = 2.593$, $p = .03$, $r = 0.31$). However, planned contrasts conducted to account for heterogeneity (Maxwell and Delaney,2004) did not reveal any significant comparisons. see Table 2.18 above for means, SEMs.

After controlling for baseline scores, there was a significant difference in the overall RTs at post-treatment between the treatment groups ($F(5,120) = 3.296$, $p = .008$, $r = 0.29$). However, a set planned contrasts did not reveal any significant comparisons. See Table 2.18 above for means, SEMs.

After controlling for baseline scores, there was a significant difference in the correct response RTs at post-treatment between the treatment groups ($F(5,120) = 3.371$, $p = .008$, $r = 0.30$). However, a set planned contrasts did not reveal any significant comparisons. See Table 2.18 above for means, SEMs.

After controlling for baseline scores, there was a significant difference in the correct response RTs at post-treatment between the treatment groups ($F(5,120) = 3.937$, $p = .002$, $r = 0.34$). However, a set planned contrasts did not reveal any significant comparisons. See Table 2.18 above for means, SEMs.

After controlling for baseline scores, there was a significant difference in the correct response RTs at post-treatment between the treatment groups ($F(5,121) = 2.306$, $p = .049$, $r= 0.24$). However, a set planned contrasts did not reveal any significant comparisons. See Table 2.18 above for means, SEMs.

2.3.5.10.1 Summary of Picture Recognition Results

For six out of the seven picture recognition tasks there were significant effects of treatment, however none of these were seen to have significant post hoc planned comparisons. In terms of the secondary aim of this study, glucose ingestion had no impact on episodic memory for pictures.

2.4 Discussion

2.4.1 Summary of Main Findings

The primary aim of this chapter was to begin to investigate whether the inconsistencies in the glucose enhancement literature may be mediated by differences in drink compositions. This chapter assessed the efficacy of the ingredients of experimental and placebo drinks to ascertain whether these ingredients are, as previously assumed, inert. Previous research exploring the effects of glucose ingestion on cognition, particularly those studies investigating the *glucose enhancement of memory effect,* have been based on the premise that the only active ingredient of these experimental and placebo drinks was the glucose dose. Importantly, as all ingredients were being tested in isolation, the secondary aim of this chapter was to give insight into the effects of a standard 25g glucose dose in its pure form, diluted in 200mls water, in comparison to each individual treatment ingredient.

In terms of memory enhancement one of the research questions posed by this chapter investigated whether this effect would be mediated by differing drink ingredients. No effects of treatment were seen for free recall of presented words or for word recognition tasks. However, for some measures of the Stroop tasks, lemon juice was seen to mediate faster response RTs when compared with the water control. Correct responses to the 'choice reaction' task were significantly less in the lemon juice condition relative to the water control. Glucose and RSFOC were seen to mediate the number of correct subtractions performed for the Serial 7's task in comparison to the water control. Episodic memory tasks also saw effects of treatment, post treatment correct responses to word recognition and multiple measures of the picture recognition task were impacted by treatment although again the post hoc planned contrasts were non-significant.

2.5 Primary Outcomes

In terms of the mixed results of previous research, which had explored the glucose enhancement of memory effect, this chapter set out to investigate whether this effect was mediated by differences in experimental and placebo drink compositions. There is some very tentative evidence of this for some tasks within this study, although in terms of the small number of significant comparisons across the different tasks it is possible that type 1 errors may be occurring. Lemon juice however was seen to have a significant impact on both the Stroop and Choice Reaction Time tasks which both target attentional resources. Lemon juice was seen to speed up response RTs for the Stroop task and for the choice reaction time task, lower percentages of correct judgement were made compared to water. There was only one incidence of glucose effects, with more correct Serial 7's subtractions being seen compared to water. In terms of lemon juice, as this is commonly used as a flavour mask, used in both the experimental and placebo drink, this may potentially have implications in terms of the reliability of these data. However, whilst this implies that lemon juice is influencing cognition, this may not be generalisable to the glucose literature where lemon juice was not administered in isolation. Speculatively, the effects seen here may be cancelled out by other factors such as sweetness. This outcome also provides evidence for the second research question asked here, indicating that the effect of glucose administration may be changed by the type of flavour mask used. There were no effects of glucose seen across any of the other cognitive domains targeted by the current study.

Based on the findings across the glucose enhancement of cognition literature (see section 1.5 for a detailed review of these), the expectation of this chapter was that glucose would be seen to enhance tasks which targeted memory, most specifically episodic memory, and attention/psychomotor performance. Minimal glucose effects were seen, only occurring for the correct number of serial 7 subtractions made. This supports the premise that working memory and executive function (as measured in serial 7 subtraction task) may be facilitated by glucose.

A possible explanation for the lack of glucose effects may be that the exploratory battery of tasks used in this chapter were not difficult enough, and in view of the fact that participants were university students, whilst this was not explored in the data, a 'ceiling effect' may have prevented the detection of a positive effect.

Furthermore, this chapter investigated the potential effects of so-called inert substances, such as the non-nutritive sweeteners used in placebo drinks. Tentative evidence suggests that lemon juice is not inert across all cognitive performance, influencing accuracy (choice reaction time task) and response speed (Correct Stroop RT). The mechanism for this is unclear but highlights the potential cognitive moderations of presumed cognitively inert flavour masks/placebo ingredients. However, it must be noted that while lemon juice was seen to speed RTs for the Stroop task, this may also have been due to familiarity with performing the task.

2.6 Secondary Outcomes

Given that treatment ingredients were administered in isolation, the secondary aim of this chapter was to examine the effects of a standard 25g glucose dose, in its pure form, without the potential effects of additives. The enhancement effect of glucose has commonly been reported by studies investigating episodic memory although there have been mixed results, particularly for word recognition memory. It should be noted here that whilst the word recognition task conducted in this chapter did not differentiate between the recollection and familiarity components of recognition memory, there were no effects of glucose seen on word recognition. However, effects of glucose were seen, with an increased number of correct calculations being performed for the Serial 7's task. A summary of the effects of drink ingredients on accuracy and response reaction times x domain can be seen in Table 2.19 below.

Table 2.19 Domain specific effects of individual treatments shown for accuracy and Response reaction time.

Cognitive Domain	Glucose 25g	Saccharin 5 x tablets	Aspartame 5 x tablets	Robertson's Sugar Free Orange 20ml	Lemon Juice 10ml
Episodic Memory/Accuracy	x	x	x	x	x
Episodic Memory/Reaction Time	x	x	x	x	x
Attention/ Response Inhibition/Accuracy	x	x	x	x	x
Attention/Response Inhibition/Reaction Time	x	x	x	x	Yes
Psychomotor Performance/Attention/Accuracy	x	x	x	x	Yes
Psychomotor Performance/Attention/Reaction Time	x	x	x	x	x
Working memory/Executive function/Accuracy	Yes	x	x	Yes	x
Attention & Vigilance/Accuracy	x	x	x	x	x
Attention & Vigilance	x	x	x	x	x
Executive Function/Accuracy	x	x	x	x	x
Executive Function/Reaction Time	x	x	x	x	x

2.7 Limitations

One of the limitations of this chapter was that, as this experiment was conducted as part of a learning experience, smokers were not excluded. As nicotine is known to influence glucose tolerance (see 1.3.5 for more information on this topic) and is a known risk factor for insulin resistance and the potential to develop T2DM. An additional, and related limitation to the inclusion of smokers, is that blood glucose measures were not assessed. As smoking is a known risk factor for poor glucoregulation (see section 1.3.5) it may be that the results of this study were influenced by the inclusion of smokers' data (smokers = 29; non-smokers = 101). The potential confounding effects of including smokers will be eliminated from chapter 3, by not including the data from individuals who had identified as smokers in the analyses. The high number of female participants (114 females, 16 males),a common recruitment issue amongst psychology cohorts, may also have impacted on the study. A further limitation may be whilst participants were not asked to fast prior to attending the study session, asking participants to complete a food diary for the morning of testing could have provided insight into their normal consumption habits.

2.8 Conclusion

Chapter 2 investigated the efficacy of the added ingredients of experimental and placebo treatments, by ascertaining whether these ingredients are, as previously assumed, cognitively inert. Significant effects of treatment were found the cognitive domain of attention/response inhibition mapped by the Stroop task. In terms of episodic memory, there were no treatment effects in relation to attention/response inhibition, targeted by the Stroop task, lemon juice showed faster RTs. Based on the tentative evidence from this chapter, with lemon juice speeding up RTs this finding may go some way to explain the contradictory findings in studies where lemon juice has been administered as a flavour masking agent in both the experimental and the placebo treatments (see above Table 2.1 for some examples of these) and have potentially been impacting on the facilitation of a glucose effect.

Significant effects of treatment ingredients on cognitive domains seen in this chapter are summarised in Table 2.19 above. Additionally, significantly higher levels of mental energy were seen in the aspartame condition from self-report on subjective state scales, although this isolated incidence may be a type 1 error rather than a robust effect.

A possible explanation for the effect of lemon juice may be as a result of flavonoid ingestion (Alharbi et al., 2015) although, as the flavonoid content of the acute dose of 10 ml used in the current study, an impact of flavonoids on cognition in this instance is unlikely. Alternatively, lemon juice may be linked to the perception of a refreshing taste, and as such the increased response times may be the result of enhanced levels of cortical activity triggered by trigeminal neurons in response to this refreshing taste (Eccles, 2000). These explanations of faster response times following lemon juice ingestion are attractive, since the mechanisms underlying the effect of lemon juice on RTs appear to be sensory, rather than dose related (Patapoutian et al., 2003). Chapter 2 findings suggest that some conflicting outcomes found across the glucose literature may be occurring where lemon juice has been employed as a flavour masking agent; effects of lemon juice may be modulating any potential effects of glucose on cognition.

Robinsons No Added Sugar Orange Cordial was the other flavour masking agent investigated in this study, containing citrus, aspartame and saccharin non-nutritive sweeteners, and in respect of the reported findings in the literature concerning aspartame (Linseth, et al., 2014; Konen, et al., 2000) and citrus (Alharbi et al., 2015; Labbe et al., 2011) it warranted investigation. In its role as a flavour mask containing a citrus ingredients, RNASOC, may have benefitted from the refreshing taste

perception (Labbe et al., 2011) whereas conversely some participants may have found it more palatable or familiar tasting than lemon juice as RNASOC is a common drink in the UK. However, as this study found a single effect of RNASOC, the possibility of a type 1 error may be in play here.

Considering the non-nutritive sweeteners investigated here, previous research has suggested that aspartame is not cognitively inert (Konen et al., 2000; Lindseth et al., 2014) however, with the exception of participants having higher levels of 'mental energy' in the aspartame condition, this was not supported by the findings of this chapter. However, it is suggested that the perception of sugar consumption created by aspartame ingestion can evoke changes in blood glucose levels (Melanson et al., 1999). This concept may explain the higher levels of mental energy reported in the aspartame condition; Where aspartame has been employed as a non-nutritive sweetener in placebo treatments across the glucose enhancement literature (see Table 2.1 for some examples), there is the possibility that it may be having an impact on outcomes. In terms of the other non-nutritive sweetener investigated here, no effects were seen in the saccharin condition.

Some previous research has reported glucose enhancement effects in episodic memory and attention/ response inhibition domains. However, there are suggestions in the literature that glucose enhancement is more reliably seen for more demanding tasks which have an increased cognitive load such as the performance of a secondary task during encoding (Foster, Lidder, & Sünram-Lea, 1998; Scholey, MacPherson, Sünram-Lea, Elliott, Stough, Kennedy, et al., 2013; Sünram-Lea, Foster, Durlach, & Perez, 2001; Sünram-Lea, et al., 2002). This divided attention paradigm suggests that increased cognitive demand utilises increases amounts of blood glucose (Kennedy & Scholey, 2000; Scholey, Sunram-Lea, et al., 2009; Scholey, et al., 2001). An effect of glucose was seen in this chapter with increased accuracy for the Serial 7's subtraction task which targeted working memory and executive function, but not for any of the tasks targeting episodic memory. As the purpose of the task battery used here was to assess treatment ingredients across several cognitive domains, it may be argued that tasks were not sufficiently demanding to elicit an effect of glucose or alternatively, that a glucose effect is unlikely to be seen in unfasted participants. However, whilst tasks which increase the cognitive load were beyond the scope of this chapter, further research utilising divided attention methodologies may add some clarity to current findings. Whilst the lack of a designated fasting period may be seen as a limitation, participants were tested in their natural state giving greater insight to real world application. Baseline cognitive performance was also measured which is uncommon within the glucose literature. To an extent, collecting data at baseline and then

subsequently at post-treatment compensates for the lack of fasting as participants are being tested in a more natural state of homeostasis. For future research, a methodology which addresses fluid intake and monitors changes in body mass may elucidate the effects of hydration on the absorption and utilisation of glucose. Speculatively, in terms of the inconsistent outcomes across the glucose enhancement literature, it may be argued that some combinations of treatment ingredients may have been modulating or exaggerating the glucose enhancement effect. To better understand which treatment composition is the most appropriate for investigating the potential effects of glucose on cognition, chapter 3 will move forward by investigating the effects of commonly used combinations of experimental and placebo treatments.

3 Investigation of Combined Treatment Ingredients: Does Glucose Administration Mediate Episodic Memory and Inhibition Processes?

3.1 Introduction

The primary aim of Chapter 2 was to further explore the efficacy of the various ingredients found in experimental and placebo treatments across the glucose and glucoregulation related literature. Chapter 2 questioned whether the mixed results seen in the glucose enhancement literature may be because some of these previous outcomes had been mediated by what are thought to be inert drink ingredients, such as flavour-masks and non-nutritive sweeteners. The between-subjects design used in chapter 2 to examine the effects of six treatment ingredients in isolation, also enabled the secondary aim of the chapter, which was to explore the effects of a 25g dose of ingested glucose in its pure form, without any interference from potentially active flavour-masking ingredients, which would normally be used in both experimental and placebo treatments. There is also speculation in the glucose literature concerning the range of cognitive domains that may be modulated by this effect; chapter 2 addressed this using an array of cognitive tasks which *a priori* literature had suggested were domain specific.

Chapter 2 found evidence suggesting that lemon juice may selectively speed reaction times (RTs) in the Stroop task and reduce accuracy in a choice reaction task. . In the RSFOC condition performance on the serial 7s subtraction task was improved. This highlights that these drink ingredients are not cognitively inert, potentially underpinning some inconsistencies in the literature that may have been influenced by treatment ingredients rather than a direct glucose effect. However, to further explore the efficacy of treatment ingredients, and introducing the possibility that certain combinations of these ingredients may also be an issue, chapter 3 addressed this question using six combinations of experimental and placebo treatments that are widely used in the literature (see section 3.2.3 for treatments used in this chapter).

With regards to the secondary aim of chapter 2, whilst glucose was not seen to modulate episodic memory, evidence from a systematic review suggests that glucose enhancement of memory performance in healthy young adults is more sensitive to an acute glucose dose than were other cognitive domains (Hoyland et al., 2008). To further explore this Chapter 3 focused on episodic

memory, specifically episodic memory for emotional words and additionally, recognition of emotionally valenced pictures.

Investigation of recognition memory allows exploration of the dual process model (for a review see Yonelinas, 2002) which proposes that 'recollection' and 'familiarity' operate as two different processes (Aggleton & Brown, 2006; Rugg & Yonelinas, 2003; Woodruff et al., 2006b). For a more detailed description of the dual-process model see section 1.5.2.6.1. There is a profusion of literature which suggests that acute glucose administration facilitates verbal episodic memory in healthy young adults (for review articles see Messier, 2004; Riby, et al., 2004; Smith, Riby, et al., 2011). One theoretical explanation is that this enhancement is subserved by the hippocampus (Riby & Riby, 2006), (see section 1.5.2.6.1.1 for a more in depth discussion of this hypothesis) and whilst facilitating the hippocampally mediated recollection component, no enhancement is seen for the familiarity component of recognition memory which is subserved by the perirhinal cortex (see section 1.5.2.6.1.1 for more detail). However, there is an equally convincing line of research which suggests that glucose effects are only seen under conditions of increased cognitive demand and that these enhancements are mediated by a more global modulation of attentional resources (see section 1.5.2.6.1.1 for a more detailed discussion).

Chapter 3 investigates whether a glucose enhancement effect can be observed by manipulating the emotionality of stimuli. Previous research has found that emotionally valenced pictures and narrative improves memory and revealed that was +6% increase in the blood glucose levels of fasted individuals following a saccharin placebo treatment (Parent et al., 1999). A further study, Scholey et al. (2006), explored the effects of emotionality on circulating blood glucose levels, using neutral and negatively valenced stimuli in a word recall task. No glucose dose was administered in this study and the authors found that blood glucose levels were elevated for emotional words compared to neutral words at post-test, although no memorial advantage was seen for the emotional words. A between-subjects study asking participants to rate the arousal rating of either neutral or emotionally valenced pictures, found that the group who were rating the emotional pictures, correctly recalled more pictures and also had higher circulating blood glucose levels (Blake et al., 2001). Given that the hippocampus is heavily populated with insulin receptors and involved in the encoding and retrieval processes of episodic memory, it may be that the memorial advantage conveyed by emotionally valenced stimuli is driven by this elevation of glucose levels. Previous work suggested that the glucose facilitation of memory for positive and neutral, but not negative words, is diminished by the

presence of a secondary task (Bonner & Elliott, Unpublished). This may suggest that the emotionality of the stimuli may mediate the role of glucose ingestion on memory as the emotionality of the stimuli may pose different encoding biases. This chapter will explore further whether potentially different mechanisms subserve memory for negative stimuli without the presence of a high-effort secondary task. To assess the effects of emotionality this chapter utilised word sets which included negative, neutral, and positively valenced words, consequentially, potentially selectively attenuating and mediating blood glucose levels.

In view of the speeded reaction times found in chapter 2 for attention/inhibition domain specific tasks in the lemon juice condition, chapter 3 incorporated Eriksen and Eriksen's (1974) Flanker Task to facilitate the exploration of treatment effects on attention and inhibition. The Flanker task is a response competition paradigm which assesses attentional and response control resources. Conflicts are initiated by the presentation of incongruent trials. The Flanker paradigm is a conflict task, commonly used as a measure of attentional control and sensorimotor processing (see section 1.5.2.3 for a detailed description of conflict tasks). Participants are asked to discriminate between target stimuli, such as left or right pointing arrows, which appear in an expected position. The target stimulus is flanked by distractor arrays which are irrelevant but are either congruent, incongruent, neutral, or signifying that no action should be taken (see **Figure 3.2** for example). Glucose has been seen to slow flanker response reaction time (Hope et al., 2013) and reaction speeds to a sustained attention task were slower following a 50 gm glucose dose (Adan & Serra-Grabulosa, 2010). Benton et al., (1994) found that glucose speeded Stroop task reaction times whereas Brown and Riby (2013) found no significant effects of glucose. Craft et al. (1994) found speeded response times and increased errors for incongruent Stroop trials following glucose, whereas Gailliot et al. (2007) found no glucose effects. Flanker task research has also explored glucose enhancement effects with two studies reporting slowed response speeds following a glucose dose. Hope et al. (2013) suggest that these slowed Flanker responses may be indicative of a non-uniform enhancement effect and argue that glucose enhancements may be domain specific. A further study using the Flanker paradigm, suggested that elevated glucose levels was slowing response speed and as such, potentially impairing sensorimotor processing (Seiss et al., 2013). Sustained attention is the capacity to remain attentive during processing of stimuli presented in a repetitive manner; the non-arousing nature of such stimuli leads to habituation which distracts the participant from the distractor arrays (Robertson et al., 1997). The secondary purpose of this task was to serve as a distractor between word encoding and word recognition phases.

Importantly, across the glucose literature, baseline assessments of cognitive performance prior to treatment consumption are rarely administered. This lack of baseline assessment may be a considerable confounding variable in glucose studies. Although participants are predominantly tested in a fasted state, factors such as the secondary meal effect, sleep quality, mood etc. may all vary across testing visits and influence performance. Chapter 2 addressed this by collecting baseline measures for all cognitive tasks and controlling for these by utilising ANCOVA analyses with baseline measure as the covariate. In the between groups design, it was important to include a baseline measure of performance so as to be confident evoked changes were due to the experimental manipulation rather than between group individual differences.

The primary aim of this chapter is to continue to investigate the anomalies in the literature concerning the effects of glucose administration on cognitive processes. Chapter 2 highlighted differential findings across experimental drink ingredients, some of which were previously considered to be cognitively inert. This chapter will explore the potential effects of these treatment ingredients in combinations commonly used in the glucose literature (see Table 3.1 for treatments). The conclusions drawn from investigating the treatment combinations will inform the choice of treatment ingredients used in the remaining studies included in this thesis. The secondary aim was to explore glucose enhancement of episodic memory for neutral and emotionally valenced words and pictures. Sustained attention and inhibition were also explored. The research questions investigated in this chapter were as follows:

- Do different combinations of experimental and placebo treatments have differential effects on episodic memory for neutral and emotional words and pictures, and attentional control?

- Do emotional stimuli, as opposed to neutral stimuli differentially impact glucose enhancement of episodic memory?

- Does ingested glucose influence episodic memory for neutral or emotional words and pictures? If glucose enhancement is driven by task demand, then recollection and familiarity of stimuli would be enhanced. On the other hand, if glucose enhancement is domain related, enhancement would facilitate recollection only.

- Is Flanker Task response control differentially mediated by ingested glucose? If there is an enhancement effect glucose ingestion would modulate the accuracy and/or response RTs of Go/NoGO responses.

3.2 Materials and Method

3.2.1 Design

A randomised, placebo controlled, single-blind between-groups design was employed. The variables were Treatment with seven drink conditions (see Table 3.1 below) and Time, baseline measures and post-treatment measures.

3.2.2 Participants

Ninety-two self-reportedly healthy adult volunteers (74 females, 18 males; mean age 21.30 years, SD 3.32) (see Appendix 3.2) took part in this study which was approved by the Staffordshire University Psychology Ethics Committee. Participants were students and as such, participation in this research formed a part of their learning experience.

Prior to taking part in the study informed consent and health and demographic screening was completed to ascertain whether prospective participants met the exclusion/inclusion criteria of the study. Participants were screened for food allergies which related to the treatments used in the study and any glucoregulatory/metabolic disorders e.g., diabetes, or phenylketonuria. All participants were asked to self-report whether they were in good health, free from prescription drugs (excluding contraceptives) over-the-counter medicines, illicit and recreational drugs (including nicotine). Demographic and morphometric information collected indicated number of years in education (mean 15.21 years, SD 0.66), BMI (mean 24.84, SD 5.70). For complete range of individual characteristics, please see

Appendix 3.1. Procedures were in place so that all students could fully participate in the learning experience, no data collected from excluded or non-consenting participants was saved.

On completing the study student received two ‘Research Participation Vouchers’. A voucher exchange scheme is operated within the Staffordshire University Psychology department which

enables students' access to the research participation voucher scheme when recruiting for their Level 6 Project studies.

3.2.3 Treatments

This chapter investigated combinations of sweeteners and flavour-masking agents commonly used in the glucose literature (see Table 3.1 below). Participants were blind to their allocated condition but were fully informed as to the ingredients used in all drinks to be consumed over the study. All drinks were prepared on the day prior to testing and were stored in sealed containers overnight in a refrigerator prior to serving. All drinks were made up to a volume of 200 ml.

Table 3.1 Treatment compositions.

Flavour Mask	Sweetener/Glucose & Dosage
20 ml Robinsons No Added Sugar Orange Cordial	25g glucose
20 ml Robinsons No Added Sugar Orange Cordial	5 Saccharin based sweeteners
20 ml Robinsons No Added Sugar Orange Cordial	5 aspartame based sweeteners
10 ml lemon juice	25g glucose
10 ml lemon juice	5 saccharin based sweeteners
10 ml lemon juice	5 aspartame based sweeteners
No Flavour Mask	Water only

Health screening forms were checked prior to handing out drinks. Drinks were mixed and labelled by the researcher the day before use and stored in a refrigerator. Drinks were randomly allocated to participants; drink bottles were covered with paper sleeves to hide the contents and participants were instructed not to discuss their drinks with other participants.

3.2.4 Task Stimuli

3.2.4.1 Word Display and Word Recognition

Three separate words lists each comprised of 60 frequency matched nouns taken from the 'Affective Norms for English Words' (Bradley & Lang, 1999). This allowed comparison with existing literature regarding the effects on episodic memory.

Each word list was unique, equal numbers of negative, neutral, and positive words. The three word lists were matched for valance ratings across the negative, neutral words and positive words. Word lists were randomised for each participant with the display blocks.

3.2.4.2 Picture Recognition

Stimuli for this task were taken from the International Affective Picture System (IAPS) (Lang et al., 1997), a set of normative photographs. Seventy-eight positive, negative, and neutral images were used, as such 39 'old' pictures for the encoding phase and 39 'new' pictures included as distractors for the recognition phase. One-way ANOVAs were employed prior to data collection to ascertain that the mean valences of negative, neutral, and positive pictures were significantly different and, that there was no significant difference across the different picture lists.

3.2.4.3 Flanker Task

A modified version of Eriksen & Eriksen's (1974) test of inhibitive processes. Left and right arrows are presented on screen, with congruent, incongruent, neutral, or no-go symbols flanking the arrow. Each block of Flankers was comprised of 100 trials and participants responded to the centre arrow, unless a 'no-go' flanker is displayed in which no response should be made.

3.2.5 Assessments of Mood and Physical and Mental State

3.2.5.1 Bond Lader Mood Assessment

Subjective measures of mood were assessed at baseline and post-test using the COMPASS Bond Lader mood scales in which participants used the mouse to indicate the point on the scale which was indicative of how they were feeling. Bond Lader (Bond & Lader, 1974) measures were taken for how 'alert', 'calm' and 'contented' participants were feeling.

3.2.5.2 Physical and Mental State Assessment

Subjective measures of physical and mental state were also taken at baseline and post-test using the COMPASS Visual Analogue Scales, following on from the Bond Lader assessments. Participants used the mouse to indicate the point on the scale which was indicative of how they were feeling. Physical and mental state assessments were collected for participants' levels of 'mental energy', 'concentration', 'fullness', 'physical stamina', mental fatigue', 'hunger', 'mental stamina', 'physical tiredness', 'thirst', 'mentally tired'.

3.2.6 Cognitive Assessments

Prior to the experiment participants received training in each of the cognitive tasks (see Figure 3.1 (a) below). The task practice block of tests was comprised of, word display x 12 old words, Flanker task x 2 minutes, word recognition x 6 old and 6 novel words, picture task encoding 6 old and picture recognition x 6 old and 6 novel words. Cognitive task assessments were presented in three 'blocks', see Figure 3.1(b) below, the baseline and post-treatment assessments were the same format but with different sets of words and pictures being used. The Flanker task and the picture recognition task acted as distraction/filler tasks between the word recognition encoding and recognition tasks. The study format here was piloted with the intention of employing a similar pattern of tasks for the chapter 4 EEG study. Screen images of task instructions and examples can be seen below in **Error! Reference source not found.**

Figure 3.1 Schematic of (a) task practice block and (b) cognitive assessment task order

a) Practice Block of Tests Performed

Practice Set of Tests				
With verbal and Onscreen Instruction				
Word display Encoding	Flanker Task	Word Recognition	Picture Display (Encoding)	Picture Recognition

b) Order of Assessments

Baseline Bond Lader & Physical and Mental State Scales	Baseline Assessments											
	COGNITIVE ASSESSMENTS BLOCK ONE				COGNITIVE ASSESSMENTS BLOCK TWO				COGNITIVE ASSESSMENTS BLOCK THREE			
	Word display Encoding of 1st Word List	Flanker Task	Word Recognition of 1st Word List	Picture Display (Encoding)	Word display Encoding of 2nd Word List	Flanker Task	Word Recognition of 2nd Word List	Picture Recognition	Word display Encoding of 3rd Word List	Flanker Task	Word Recognition of 3rd Word List	
Post-Treatments Assessments												Post-Test Bond Lader & Physical and Mental State Scales
COGNITIVE ASSESSMENTS BLOCK ONE					COGNITIVE ASSESSMENTS BLOCK TWO				COGNITIVE ASSESSMENTS BLOCK THREE			
Word display Encoding of 1st Word List	Flanker Task	Word Recognition of 1st Word List	Picture Display (Encoding)	Word display Encoding of 2nd Word List	Flanker Task	Word Recognition of 2nd Word List	Picture Recognition	Word display Encoding of 3rd Word List	Flanker Task	Word Recognition of 3rd Word List		

3.2.6.1 Word Display Encoding

For each of the six encoding phases (three at baseline and 3 at post-treatment), participants were presented with thirty words (10 each of negative, neutral, and positive words), displayed on screen for 2 seconds each with a 1 second interval (blank screen) between words. Words shown in the encoding phase are referred to as 'old' words. A modified Flanker task was employed as a filler task between word encoding and word recognition.

3.2.6.1 Flanker Task

Participants were presented with an inhibition task which also serve as a word retention filler task between word encoding and recognition phases. A modified version of Eriksen's Flanker Task Eriksen & Eriksen, 1974) was used. Each Flanker block comprised of 100 trials, random presentations of 8 Flanker conditions. Left and right arrows were presented on screen, with congruent, incongruent, neutral, or no-go symbols flanking the central arrow. For this Go/No Go task correct responses were weighted toward a key-press response, with 75% being 'Go' and 25% 'No Go' responses. Participants responded to the direction of the central arrow using the left and right keys on the keyboard, unless a 'no-go' flanker, for which the central arrow was flanked crosses, was displayed; in which no response should have been made. The purpose of this task was to explore inhibition processes, giving both a speed and an accuracy score. There were eight different Flanker types namely, left, and

right congruent, left and right incongruent, left and right neutral and left and right No-Go, see **Figure 3.2** for examples. The random presentation of the differing Flanker direction arrows created a conflict which tested inhibition and attention. Images were presented at the centre of a blank screen for 500 milliseconds with a 900 millisecond interstimulus gap.

Figure 3.2 Flanker Task. Instruction screen and example of onscreen 'left' flanker images.

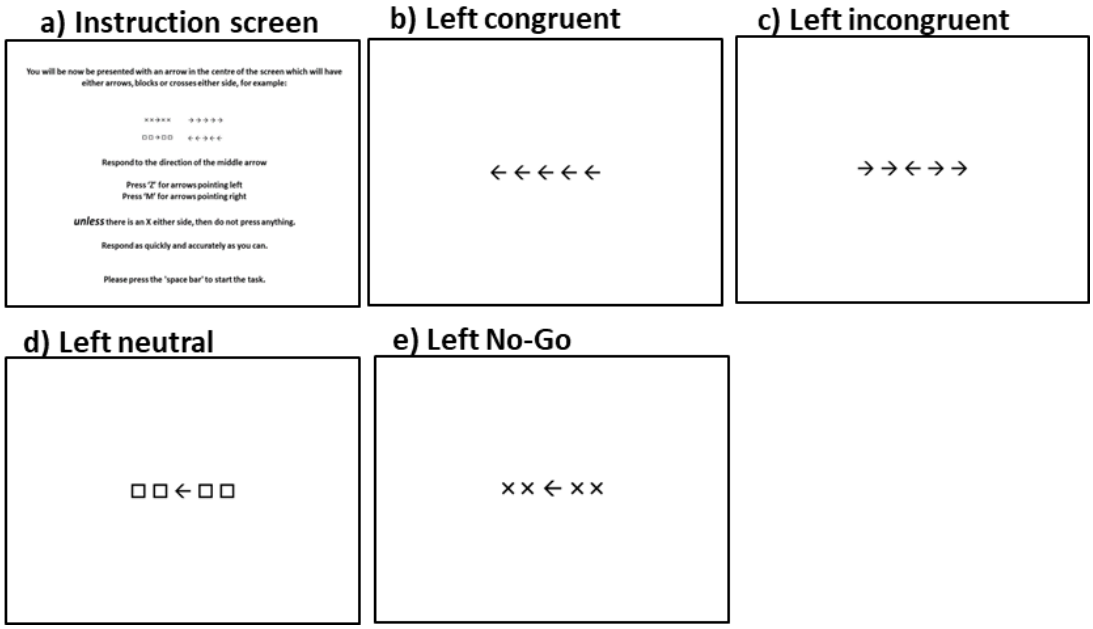
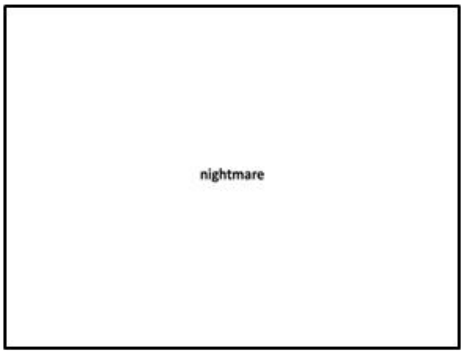


Figure 3.3 Cognitive assessments screen examples. N.B. To protect the integrity of IAPS images the example here is a non-IAPS, non-copyrighted item.

a) Encoding Instructions

b) Encoding example

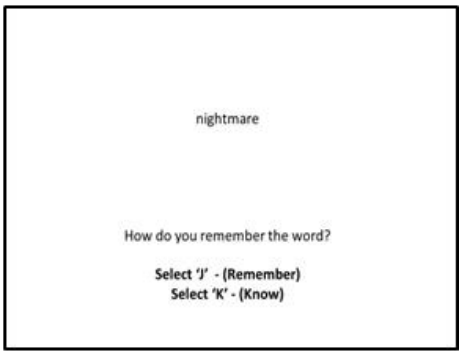


c) Flanker Task Instructions

d) Recognition Instructions

e) Recognition decision

f) 'Remember' or 'know'



g) Picture Encoding Instructions

h) Picture Example

3.2.6.2 Word Recognition

The 'word recognition' phases of the experiment explore the 'recollection' (remembering) and 'familiarity' (knowing') components of the subjective experience of recognition memory. For each Word Recognition phase participants were presented with 60 words, 30 'old' words from the Word Display and 30 'new' distractor words (all randomised). Participants were shown the 30 previously studied words randomly displayed with 30 novel words (distractors not seen during the encoding phase) and asked if they recognised the word from the related word list. If the participant responded, 'yes' they were then asked to quantify their subjective remembering experience by selecting 'J' (Remember) or 'K' (Know). For a schematic of the word recognition phase see **Figure 3.3**. The recognition task will also allow response times to be assessed. Across the three assessment blocks six different word lists were used and no words were interchangeable between blocks.

3.2.6.3 Picture Encoding

Participants were presented with thirty-nine pictures (13 each of negative, neutral, and positive words) which were displayed on screen for 2 seconds each with a 1 second interval (blank screen) between words. Pictures shown in the encoding phase are referred to as 'old' pictures. This task also served as a filler task between the word recognition and the word encoding phase of the consecutive block of tasks.

3.2.6.4 Picture Recognition

For each Picture Recognition phase participants were presented with 78 words, 39 'old' pictures from the Picture Encoding and 39 'new' distractor pictures (all randomised). Participants were shown the 39 previously studied pictures randomly displayed with 39 novel pictures (distractors not seen during the encoding phase) and asked if they recognised the picture from the related word list. If the participant recognised the picture from the encoding phase, they were asked to press the space bar. If they did not recognise the picture, they were asked to do nothing in which case the next picture would appear on the screen. Across the three assessment blocks different pictures were used and no pictures were interchangeable between blocks. The picture recognition task assessed correct recognitions of old and novel pictures.

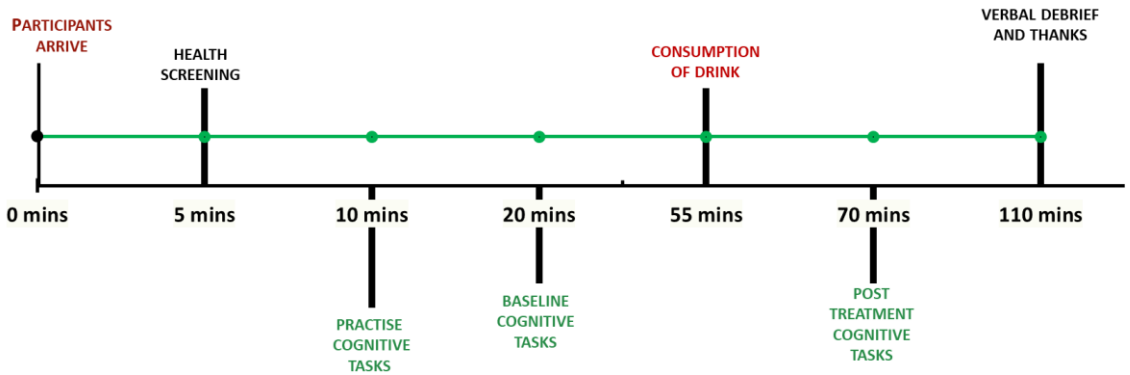
3.2.7 Procedure

Participants arrived in groups of, on average 15 per session and before the session began health screening information and informed consent was sought. Thirty-four participants attended sessions which began at 9.00 am, 47 participants attended at 11.00 am and 11 participants attended at 1.00 pm. The researcher ensured participants were clear on what was expected of them, checked the screening forms for any allergies to the drink ingredients, checked to ensure the participants met the inclusion criteria, invited questions, and reiterated that participation was voluntary.

A practice set of tests with verbal instruction as well as task related onscreen was performed to train participants on each of the tasks that were to be used. Following the practice participants completed the first set of tasks in the order shown in Figure 3.1 above to attain a baseline measure of their performance.

Each participant number was randomly assigned to one of the seven drink conditions prior to testing. Following the baseline assessment, participants were handed their allocated drink and were given 5 minutes to consume it; after the 5 minutes had lapsed the 10-minute absorption period began, during which participants were asked to sit quietly and at rest. The post-treatment assessment was then completed to ascertain whether the drinks may have influenced cognition. The structure of the sessions can be seen below in **Figure 3.4**.

Figure 3.4 Schematic of study day running order.



3.2.8 Statistics

The current chapter utilised a more complex mixed measures design than chapter 2. The complexity of the analysis meant that an ANCOVA was not appropriate. ANOVA was employed for this data.

The specific analysis for each measure is outlined in the results section.

3.2.8.1 Data Cleaning

Data was screened and cleaned prior to analysis. Where non-sensible values, missing data or outliers were found these were omitted from the analyses using listwise deletion. Datasets were checked for assumptions of between-groups ANOVA, as such, independence of scores, normal distribution and homogeneity of variance.

3.3 Results

3.3.1 Demographic Data Analysis

See Table 3.2 below for means and SEMs of participants' age, education years, and BMI.

Table 3.2 Demographic information by treatment groups and sex.

Treatment Group	Sex	N	Age (years)*			Education (years)*			BMI (kg/m^2)#			Eyesight Correction *		Handedness*	
			Mean	±	SEM	Mean	±	SEM	Mean	±	SEM	NO	YES	Right	Left
Robinson's Sugar Free & Glucose	Females	2	21.50	±	1.50	15.00	±	0.00	20.80	±	0.97	0	2	2	0
	Males	10	20.20	±	0.49	15.20	±	0.20	22.76	±	2.12	2	7	10	0
Robinson's Sugar Free & Saccharin	Females	1	19.00	±	0.00	15.00	±	0.00	29.22	±	0.00	0	1	1	0
	Males	11	20.00	±	0.23	15.27	±	0.14	26.10	±	2.45	5	6	11	0
Robinson's Sugar Free & Aspartame	Females	3	21.00	±	1.53	15.67	±	0.33	21.87	±	1.58	2	1	3	0
	Males	15	21.53	±	1.00	14.93	±	0.18	26.69	±	1.37	8	7	13	2
Lemon Juice & Glucose	Females	5	22.00	±	1.38	15.00	±	0.55	24.46	±	1.79	3	2	5	0
	Males	8	21.88	±	1.65	15.00	±	0.00	24.79	±	1.95	1	7	8	0
Lemon Juice & Saccharin	Females	1	20.00	±	0.00	15.00	±	0.00	36.02	±	0.00	0	1	1	0
	Males	9	20.11	±	0.39	15.33	±	0.17	22.56	±	1.31	8	1	9	0
Lemon Juice & Aspartame	Females	3	21.67	±	0.88	15.33	±	0.33	25.00	±	0.80	3	0	2	1
	Males	12	23.00	±	1.56	15.55	±	0.21	26.18	±	1.90	8	4	10	2
Water	Females	3	21.33	±	0.88	15.00	±	0.00	26.94	±	2.47	1	1	2	0
	Males	9	22.11	±	1.27	15.33	±	0.33	22.65	±	1.33	4	5	8	1

With the exception of eyesight correction, there were no significant differences in demographic measures between treatment groups, see Table 3.3 below for statistical justifications. Whilst there was a significant effect of treatment for eyesight correction, there were no significant Bonferroni adjusted pairwise comparisons between treatment groups.

Table 3.3 Demographic data one-way (7) Treatment ANOVAs. F values, degrees of freedom, significance levels and effect sizes are indicated.

Demographic Information	df	F	p value	r
Sex = Female	(6,91)	0.794	0.58	0.23
Sex = Male	(6,91)	0.794	0.58	0.23
Age	(6,91)	1.357	0.24	0.30
Years in Education	(6,91)	0.885	0.51	0.24
BMI	(6,91)	0.807	0.57	0.23
Handedness = Right	(6,91)	1.424	0.22	0.30
Handedness = Left	(6,91)	1.424	0.22	0.30
Eyesight correction = No	(6,91)	2.525	0.03	0.39
Eyesight correction = Yes	(6,91)	2.525	0.03	0.39

3.3.2 Bond Lader Mood Scales

See **Table 3.4** below for means and SEMs of the primary 2-way ANOVA.

Table 3.4 Bond Lader mood scales. Means, SEMs and significant effects for. Significant effects and interactions are indicated (Ti = Time, Tr = Treatment, ***p<0.001)

Outcome	Treatment	N=	Baseline			Post-Tasks			Significant Effects and Interactions
			Means	±	SEM	Means	±	SEM	
Bond Lader Alert	RNASOC/Glucose	14	44.33	±	2.56	47.48	±	3.41	
	RNASOC/Saccharin	11	44.59	±	3.70	49.52	±	4.55	
	RNASOC/Aspartame	18	47.95	±	3.28	47.43	±	3.12	
	Lemon Juice/Glucose	13	44.18	±	3.12	50.51	±	3.76	
	Lemon Juice/Saccharin	10	47.97	±	2.15	49.63	±	4.59	
	Lemon Juice/Aspartame	15	47.42	±	3.03	49.93	±	3.62	
	Water Control	14	44.21	±	3.26	44.19	±	3.99	
Bond Lader Calm	RNASOC/Glucose	14	57.54	±	3.29	48.54	±	2.15	
	RNASOC/Saccharin	11	64.95	±	2.50	55.82	±	3.41	
	RNASOC/Aspartame	18	60.36	±	2.61	52.86	±	2.64	
	Lemon Juice/Glucose	13	59.50	±	4.47	54.38	±	3.32	Ti ***
	Lemon Juice/Saccharin	10	62.60	±	4.21	58.75	±	3.86	
	Lemon Juice/Aspartame	15	58.70	±	3.65	58.93	±	2.88	
	Water Control	14	64.07	±	2.45	57.79	±	2.75	
Bond Lader Content	RNASOC/Glucose	14	51.31	±	3.66	52.29	±	3.66	
	RNASOC/Saccharin	11	53.67	±	3.32	57.18	±	3.40	
	RNASOC/Aspartame	18	56.63	±	3.69	54.91	±	3.53	
	Lemon Juice/Glucose	13	52.34	±	3.84	53.95	±	3.09	
	Lemon Juice/Saccharin	10	56.26	±	3.78	57.02	±	5.22	
	Lemon Juice/Aspartame	15	59.28	±	3.11	58.84	±	2.62	
	Water Control	14	56.11	±	2.68	54.21	±	2.75	

Two-way mixed factorial (Treatment (7) x Time (2)) ANOVAs were conducted on each of the subjective measures of 'alertness', 'contentedness', 'calmness'. None of the primary two-way interactions were found to be significant, see Table 3.5 below for statistical justifications.

Table 3.5 Bond Lader treatment x time ANOVAs. F values, degrees of freedom, significance levels and effect sizes are indicated.

Bond Lader Mood Scales	df	F	p value	r
Alertness	(6,88)	0.550	0.768	0.09
Calmness	(6,88)	1.081	0.380	0.13
Contentedness	(6,88)	0.519	0.792	0.07

3.3.2.1 Summary of Bond Lader Mood Scales

See Section 3.3.1

Mood was not affected by differences in treatment.

3.3.3 Physical and Mental State Measures

See **Table 3.6** below for means and SEMs of the primary 2-way ANOVA.

Table 3.6 VAS physical and mental state scales. Means, SEMs and significant and interactions are indicated (Ti = Time, Tr = Treatment, *p<0.05, ***p<0.001)

Outcome	Treatment	N=	Baseline			Post-Tasks			Significant Effects and Interactions
			Means	±	SEM	Means	±	SEM	
Mental Energy	RNASOC/Glucose	14	46.57	±	4.27	46.86	±	4.05	
	RNASOC/Saccharin	11	41.36	±	2.36	46.64	±	5.21	
	RNASOC/Aspartame	18	46.67	±	3.47	44.83	±	4.22	
	Lemon Juice/Glucose	13	48.54	±	3.65	50.31	±	3.41	
	Lemon Juice/Saccharin	10	47.30	±	1.84	44.40	±	4.87	
	Lemon Juice/Aspartame	15	49.73	±	2.40	48.60	±	3.06	
	Water Control	14	44.50	±	3.40	44.93	±	2.95	
Concentration	RNASOC/Glucose	14	49.50	±	4.95	47.86	±	4.31	
	RNASOC/Saccharin	11	53.55	±	3.85	52.55	±	4.75	
	RNASOC/Aspartame	18	46.33	±	4.48	45.06	±	4.97	
	Lemon Juice/Glucose	13	48.15	±	4.28	47.31	±	4.91	
	Lemon Juice/Saccharin	10	56.20	±	4.32	48.00	±	6.91	
	Lemon Juice/Aspartame	15	56.73	±	3.02	45.93	±	4.75	
	Water Control	14	42.57	±	4.06	41.21	±	5.71	
Fullness	RNASOC/Glucose	14	37.29	±	4.59	43.64	±	4.81	
	RNASOC/Saccharin	11	33.55	±	4.79	44.73	±	2.48	
	RNASOC/Aspartame	18	31.89	±	3.78	35.67	±	3.59	
	Lemon Juice/Glucose	13	40.23	±	5.91	37.77	±	4.56	Ti *
	Lemon Juice/Saccharin	10	46.60	±	4.94	49.90	±	5.19	
	Lemon Juice/Aspartame	15	44.20	±	6.43	42.47	±	6.52	
	Water Control	14	39.71	±	4.46	43.71	±	4.61	
Physical Stamina	RNASOC/Glucose	14	42.07	±	4.37	42.29	±	3.56	
	RNASOC/Saccharin	11	37.73	±	3.82	48.45	±	4.98	
	RNASOC/Aspartame	18	45.17	±	4.28	43.17	±	4.41	
	Lemon Juice/Glucose	13	48.77	±	3.64	48.92	±	4.41	
	Lemon Juice/Saccharin	10	45.50	±	2.85	45.20	±	6.28	
	Lemon Juice/Aspartame	15	47.20	±	4.15	46.87	±	5.00	
	Water Control	14	42.86	±	4.25	40.29	±	3.95	
Mental Fatigue	RNASOC/Glucose	14	61.07	±	2.86	54.14	±	4.80	
	RNASOC/Saccharin	11	52.55	±	5.75	55.91	±	4.24	
	RNASOC/Aspartame	18	60.83	±	3.73	55.17	±	4.18	
	Lemon Juice/Glucose	13	60.38	±	3.27	46.77	±	4.24	Ti *
	Lemon Juice/Saccharin	10	51.60	±	4.68	49.20	±	6.53	
	Lemon Juice/Aspartame	15	55.87	±	3.02	51.93	±	4.70	
	Water Control	14	53.57	±	3.32	52.86	±	4.72	
Hunger	RNASOC/Glucose	14	57.07	±	6.72	54.71	±	6.08	
	RNASOC/Saccharin	11	56.36	±	7.13	53.36	±	6.73	
	RNASOC/Aspartame	18	54.50	±	5.52	61.17	±	5.00	
	Lemon Juice/Glucose	13	57.46	±	4.94	58.77	±	5.46	
	Lemon Juice/Saccharin	10	44.30	±	7.10	56.60	±	5.15	
	Lemon Juice/Aspartame	15	53.07	±	6.46	54.53	±	7.19	
	Water Control	14	58.00	±	4.50	63.36	±	5.92	
Mental Satmina	RNASOC/Glucose	14	52.14	±	4.45	50.14	±	4.77	
	RNASOC/Saccharin	11	45.64	±	4.49	46.73	±	4.10	
	RNASOC/Aspartame	18	44.83	±	3.49	41.83	±	3.75	
	Lemon Juice/Glucose	13	45.08	±	3.82	50.54	±	3.83	
	Lemon Juice/Saccharin	10	51.90	±	3.48	51.60	±	5.38	
	Lemon Juice/Aspartame	15	50.07	±	3.24	46.87	±	3.91	
	Water Control	14	47.07	±	4.12	40.86	±	3.59	
Physical Tiredness	RNASOC/Glucose	14	63.79	±	4.79	53.50	±	5.50	
	RNASOC/Saccharin	11	57.82	±	5.02	58.36	±	5.21	
	RNASOC/Aspartame	18	58.61	±	4.41	54.28	±	3.89	
	Lemon Juice/Glucose	13	57.31	±	4.39	45.15	±	5.60	Ti *
	Lemon Juice/Saccharin	10	62.30	±	4.31	53.20	±	7.14	
	Lemon Juice/Aspartame	15	58.67	±	3.56	51.47	±	5.42	
	Water Control	14	61.43	±	4.60	63.79	±	4.45	
Thirst	RNASOC/Glucose	14	59.15	±	4.29	38.08	±	4.65	
	RNASOC/Saccharin	11	62.18	±	4.44	41.27	±	7.39	
	RNASOC/Aspartame	18	60.89	±	3.57	45.39	±	4.08	
	Lemon Juice/Glucose	13	62.62	±	4.79	46.00	±	4.72	Ti ***
	Lemon Juice/Saccharin	10	52.20	±	6.18	37.40	±	6.87	
	Lemon Juice/Aspartame	15	59.43	±	5.59	34.00	±	6.97	
	Water Control	14	51.00	±	4.51	36.92	±	3.63	
Mental Tiredness	RNASOC/Glucose	14	66.08	±	3.42	56.15	±	4.91	
	RNASOC/Saccharin	11	59.27	±	4.18	53.82	±	5.02	
	RNASOC/Aspartame	18	58.61	±	4.23	61.56	±	3.70	
	Lemon Juice/Glucose	13	57.38	±	3.31	51.46	±	4.61	
	Lemon Juice/Saccharin	10	62.30	±	4.91	57.30	±	6.80	
	Lemon Juice/Aspartame	15	61.43	±	4.20	53.29	±	5.28	
	Water Control	14	57.69	±	3.52	61.62	±	5.09	

Two-way mixed factorial (Treatment (7) x Time (2)) ANOVAs were conducted on each of the subjective measures of 'mental energy', 'concentration', 'fullness', 'physical stamina', 'mental fatigue', 'hunger', 'mental stamina', 'physical tiredness', 'thirst' and 'mental tiredness'. None of the primary two-way interactions were found to be significant, see Table 3.5 below for statistical justifications.

Table 3.7 Physical and mental state ANOVAs. F values, degrees of freedom, significance levels and effect sizes are indicated

Physical and Mental States	df	F	p value	r
Mental Energy	(6,88)	0.307	0.932	0.01
Concentration	(6,88)	0.600	0.730	0.11
Fullness	(6,88)	1.039	0.406	0.11
Physical Stamina	(6,88)	0.992	0.436	0.12
Mental Fatigue	(6,88)	1.177	0.326	0.15
Hunger	(6,88)	1.007	0.426	0.11
Mental Stamina	(6,88)	0.714	0.639	0.12
Physical Tiredness	(6,88)	1.351	0.244	0.14
Thirst	(6,88)	0.541	0.775	0.10
Mental Tiredness	(6,88)	1.081	0.380	0.16

Significant main effects of time were seen for fullness, mental fatigue, physical tiredness, and thirst are reported below.

3.3.4 Word Recognition Old/New

3.3.4.1 Accuracy

See Appendix 3.3 for the means and SEMs for the Word Recognition Old/New Accuracy analysis. Significant effects and interactions are indicated.

The primary four-way treatment x time x word type x valence interaction was not significant ($F(12,156) = 1.070$, $p = .389$, $r = 0.03$). Significant main effects and interactions are shown in Table 3.8 below. Only significant higher order interactions are reported in the text.

Table 3.8 Behavioural Word Recognition Old/New Accuracy ANOVA. F values, degrees of freedom, significance levels and effect sizes for interactions and main effects are shown

Main Effects/ Interactions	Df	F	p value	r
Time x Word Type x Valence	(2,156)	3.748	0.026	0.03
Word Type x Valence	(2,156)	21.432	<0.001	0.09
Time x Valence	(2,156)	13.441	<0.001	0.04
Time x Word Type	(1,78)	59.155	<0.001	0.12
Valence	(2,156)	16.57	<0.001	0.06
Word Type	(1,78)	127.885	<0.001	0.63
Time	(1,78)	6.533	0.013	0.05

There was a time x word type x valence interaction ($F(2,156) = 3.748$, $p = .026$, $r = 0.03$) (see Table 3.8 above and Table 3.9 below for interaction means and SEMs). Significant pairwise comparisons can be seen in Table 3.10 and Figure 3.5 below.

Effects of time revealed that for old words, across all three valence types, there were more correct recognitions at baseline than at post-treatment. For new negative and new positive words, there were more correct rejections at post-treatment compared to baseline. Effects of word type showed greater accuracy for (rejecting) new words compared to accuracy for (correctly recognizing) old words overall. At post-treatment, there were more correct rejections of new neutral words compared to correct rejections of both new negative and new positive words.

Effects of valence showed that at baseline old negative word responses were more accurate than old positive word responses, with baseline new neutral word responses more accurate than both positive and negative new word responses.

Table 3.9 Behavioural Word Recognition Old/New Accuracy. Means and SEMs depicting the time x word type x valence interaction

Time	Word Type	Valence	Mean	±	SEM
Baseline	Old Word	Negative	67.486	±	2.103
		Neutral	64.263	±	2.4
		Positive	61.278	±	2.17
	New Word	Negative	84.337	±	1.515
		Neutral	93.469	±	1.031
		Positive	85.041	±	1.621
Post Treatment	Old Word	Negative	57.211	±	2.028
		Neutral	55.976	±	2.677
		Positive	57.516	±	2.323
	New Word	Negative	88.014	±	1.343
		Neutral	94.027	±	0.994
		Positive	90.192	±	1.325

Figure 3.5 Behavioural Word Recognition Old/New Accuracy. Three-way time x word type x valence interaction. Figure key shows pairwise comparisons and significance levels. ***(*p < .05,**p<.005, ***p<.001 Bars show standard error.)***

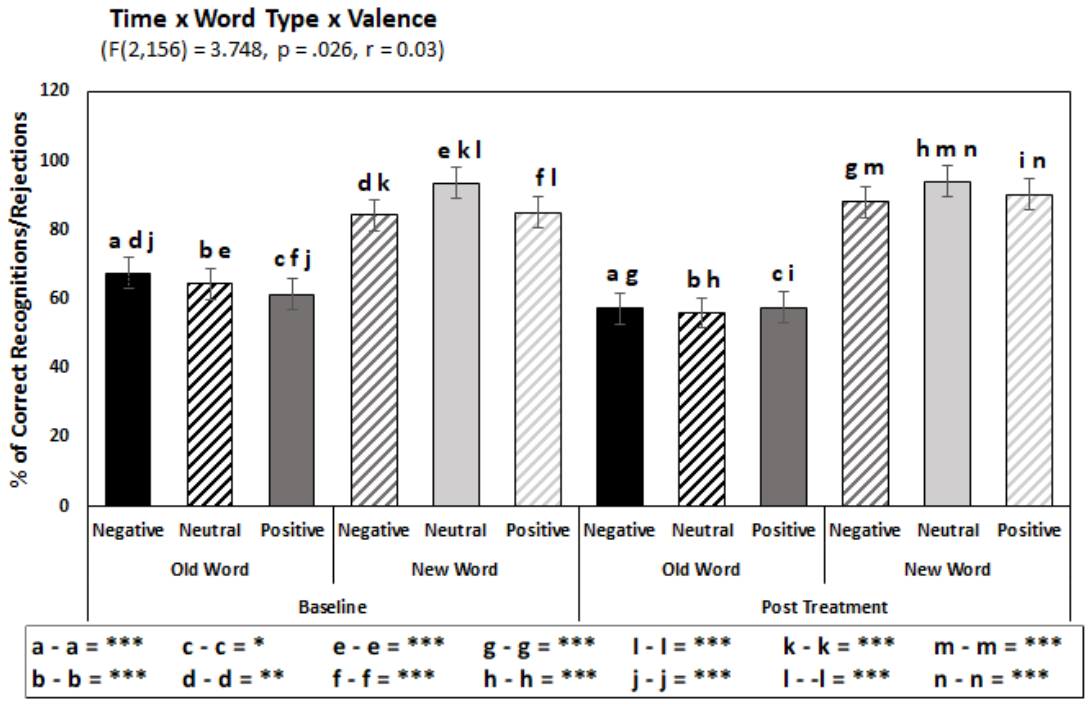


Table 3.10 Word Recognition Accuracy. Significant pairwise comparisons for the three-way time x word type x valence interaction. Condition, pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition	Pairwise Differences in Accuracy	Mean(SEM)	t(78)=	p Value
Old Words, Negative	Baseline > Post-Treatment	Baseline (Mean 67.49, SEM 2.10) Post-Treatment (Mean 57.21, SEM 2.03)	5.825	<0.001
Old Words, Neutral	Baseline > Post-Treatment	Baseline (Mean 64.26, SEM 2.40) Post-Treatment (Mean 55.98, SEM 2.67)	5.528	<0.001
Old Words, Positive	Baseline > Post-Treatment	Baseline (Mean 61.28.08, SEM 2.17) Post-Treatment (Mean 57.52, SEM 2.32)	2.245	0.028
New Words, Negative	Post-Treatment > Baseline	Baseline (Mean 84.34, SEM 1.52) Post-Treatment (Mean 88.01, SEM 1.34)	3.310	0.001
New Words, Positive	Post-Treatment > Baseline	Baseline (Mean 85.04, SEM 1.62) Post-Treatment (Mean 90.19, SEM 1.33)	5.394	<0.001
Baseline, Negative	New Words > Old Words	Old Words (Mean 67.49, SEM 2.10) New Words (Mean 84.34, SEM 1.51)	5.959	<0.001
Baseline, Neutral	New Words > Old Words	Old Words (Mean 64.26, SEM 2.40) New Words (Mean 94.47, SEM 1.03	11.229	<0.001
Baseline, Positive	New Words > Old Words	Old Words (Mean 61.28, SEM 2.17) New Words (Mean 85.05, SEM 1.62)	8.026	<0.001
Post-Treatment, Negative	New Words > Old Words	Old Words (Mean 57.21, SEM 2.03) New Words (Mean 88.01, SEM 1.34)	11.563	<0.001
Post-Treatment, Neutral	New Words > Old Words	Old Words (Mean 55.98, SEM 2.67) New Words (Mean 94.03, SEM 0.99)	12.996	<0.001
Post-Treatment, Positive	New Words > Old Words	Old Words (Mean 57.52, SEM 2.32) New Words (Mean 90.19, SEM 1.33)	11.092	<0.001
Baseline, Old Words	Negative Words > Positive Words	Negative Words (Mean 67.49, SEM 2.10) Positive Words (Mean 61.28, SEM 2.17)	4.369	<0.001
Baseline, New Words	Neutral Words > Negative Words	Neutral Words (Mean 93.47, SEM 1.03) Negative Words (Mean 84.34, SEM 1.51)	9.187	<0.001
Baseline, New Words	Neutral Words > Positive Words	Neutral Words (Mean 93.47, SEM 1.03) Positive Words (Mean 85.04, SEM 1.62)	7.545	<0.001
Post-Treatment, New Words	Neutral Words > Negative Words	Neutral Words (Mean 94.03, SEM 0.99) Negative Words (Mean 88.01, SEM 1.34)	6.410	<0.001
Post-Treatment, New Words	Neutral Words > Positive Words	Neutral Words (Mean 94.03, SEM 0.99) Positive Words (Mean 90.19, SEM 1.33)	4.324	<0.001

3.3.4.2 Response Reaction Time

See Appendix 3.4 for the means and SEMs for the Word Recognition Old/New Response Reaction time analysis. Significant effects and interactions are indicated.

The primary four-way treatment x time x word type x valence interaction was not significant ($F(12,156) = 0.491$, $p = .918$, $r = 0.03$). Significant main effects and interactions are shown in Table 3.11 below. Only significant higher order interactions are reported in the text.

Table 3.11 Word recognition Old/New Response Reaction Time ANOVA. F values, degrees of freedom, significance levels and effect sizes for interactions and main effects are shown.

Main Effects/ Interactions	Df	F	p value	r
Time x Word Type x Valence	(2,156)	3.332	0.042	0.03
Word Type x Valence	(2,156)	5.088	0.007	0.04
Valence	(2,156)	27.408	<0.001	0.11
Word Type	(1,78)	73.118	<0.001	0.31
Time	(1,78)	199.677	<0.001	0.32

There was a significant time x word type x valence interaction ($F(2,156) = 3.332$, $p = .042$, $r = 0.03$) (see Table 3.11 above and Table 3.12 below for interaction means and SEMs). Significant pairwise comparisons are summarised in Table 3.13 and Figure 3.6 below.

Effects of time showed that for both old and new word types, response times to negative, neutral and positive words were faster at post-treatment than baseline.

Effects of word type showed that for both baseline and post-treatment, responses to negative, neutral, and positive words were faster for new words relative to old words.

Finally, valence effects showed that baseline response times were faster for old neutral words relative to old negative words. For new words, faster responses were made to neutral words relative to both negative and positive words. Additionally at post-treatment, both old neutral and old positive words had faster responses compared to old negative words. At post-treatment new words elicited faster responses to neutral compared to both negative and positive words.

Table 3.12 Word recognition Old/New response reaction times means and SEMs depicting the 3 way time x word type x valence interaction.

Time	Word Type	Valence	Mean	±	SEM
Baseline	Old Words	Negative	1507.338	±	45.877
		Neutral	1441.83	±	48.475
		Positive	1505.746	±	52.463
	New Words	Negative	1290.429	±	38.44
		Neutral	1134.027	±	34.648
		Positive	1287.801	±	39.699
Post Treatment	Old Words	Negative	1289.652	±	38.09
		Neutral	1197.975	±	39.588
		Positive	1213.84	±	36.795
	New Words	Negative	1001.854	±	25.218
		Neutral	927.428	±	25.086
		Positive	1016.748	±	32.474

Figure 3.6 Word recognition response reaction time. Pairwise comparisons from the 3 way time x word type x valence interaction. Figure key shows pairwise comparisons and significance levels. *(*p < .05,p<.005, ***p<.001)* Bars show standard error.**

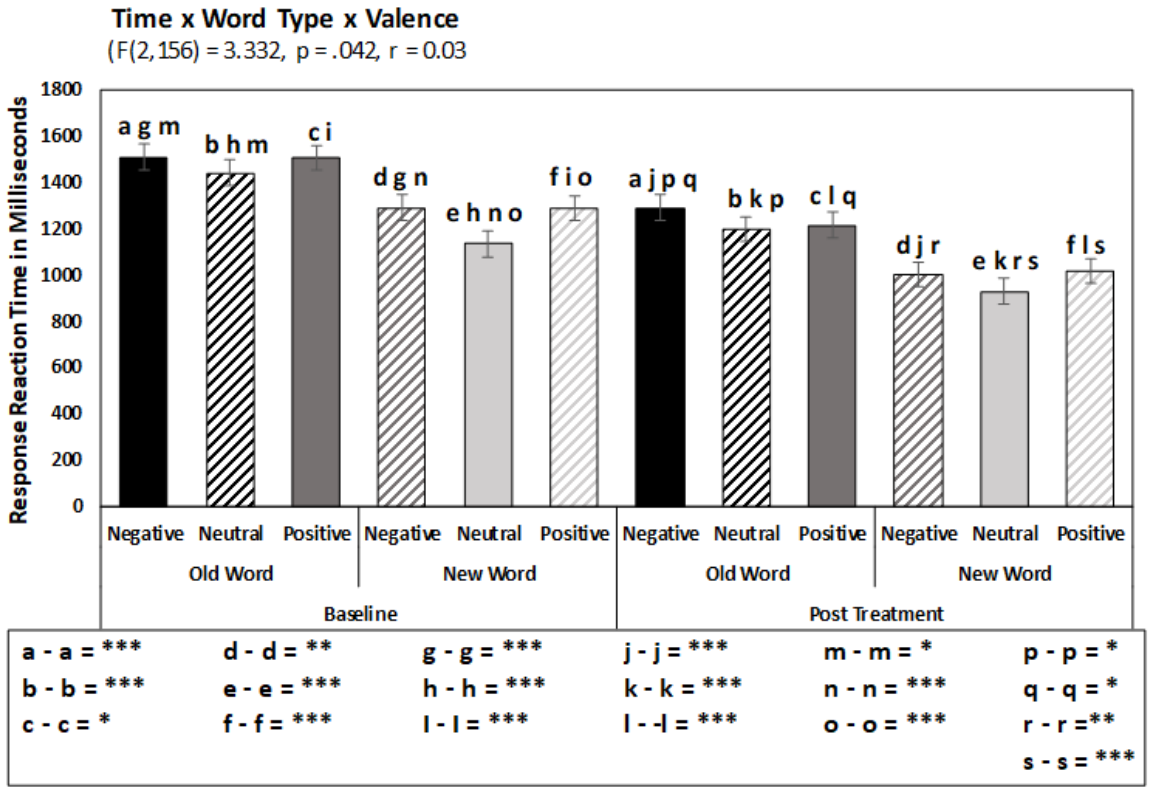


Table 3.13 Word recognition response reaction time. Significant pairwise comparisons for the three-way time x word type x valence interaction. Group, pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition	Pairwise Differences in Reaction Time	Mean(SEM)	t(77)=	p Value
Old Words, Negative	Post-Treatment faster than Baseline	Baseline (Mean 1507.34, SEM 45.88) Post-Treatment (Mean 1289.65, SEM 38.09)	7.859	<0.001
Old Words, Neutral	Post-Treatment faster than Baseline	Baseline (Mean 1441.83, SEM 48.75) Post-Treatment (Mean 1197.98, SEM 39.59)	8.223	<0.001
Old Words, Positive	Post-Treatment faster than Baseline	Baseline (Mean 1505.75, SEM 52.46) Post-Treatment (Mean 1213.84, SEM 36.80)	8.478	<0.001
New Words, Negative	Post-Treatment faster than Baseline	Baseline (Mean 1290.43, SEM 38.44) Post-Treatment (Mean 1001.85, SEM 25.22)	9.652	<0.001
New Words, Neutral	Post-Treatment faster than Baseline	Baseline (Mean 1134.03, SEM 34.65) Post-Treatment (Mean 927.43, SEM 25.09)	8.775	<0.001
New Words, Positive	Post-Treatment faster than Baseline	Baseline (Mean 1287.80, SEM 39.70) Post-Treatment (Mean 1016.75, SEM 32.47)	9.388	<0.001
Baseline, Negative	New Words faster than Old Words	Old Words (Mean 1507.34, SEM 45.88) New Words (Mean 1290.43, SEM 38.44)	5.335	<0.001
Baseline, Neutral	New Words faster than Old Words	Old Words (Mean 1441.83, SEM 48.48) New Words (Mean 1134.03, SEM 34.65)	7.205	<0.001
Baseline, Positive	New Words faster than Old Words	Old Words (Mean 1505.75, SEM 52.46) New Words (Mean 1287.80, SEM 36.70)	4.925	<0.001
Post-Treatment, Negative	New Words faster than Old Words	Old Words (Mean 1289.65, SEM 38.09) New Words (Mean 1001.84, SEM 25.22)	8.913	<0.001
Post-Treatment, Neutral	New Words faster than Old Words	Old Words (Mean 1197.98, SEM 39.59) New Words (Mean 927.43, SEM 25.09)	7.790	<0.001
Post-Treatment, Positive	New Words faster than Old Words	Old Words (Mean 1213.84, SEM 33.80) New Words (Mean 1016.75, SEM 32.47)	7.313	<0.001
Baseline, Old Words	Neutral Words faster than Negative Words	Neutral Words (Mean 1441.83, SEM 48.76) Negative Words (Mean 1507.34, SEM 45.88)	2.585	0.035
Baseline, New Words	Neutral Words faster than Negative Words	Neutral Words (Mean 1134.03, SEM 34.65) Negative Words (Mean 1290.43, SEM 38.44)	6.239	<0.001
Baseline, New Words	Neutral Words faster than Positive Words	Neutral Words (Mean 1134.03, SEM 34.65) Positive Words (Mean 1287.80, SEM 36.70)	5.717	<0.001
Post-Treatment, Old Words	Neutral Words faster than Negative Words	Neutral Words (Mean 1197.98, SEM 39.59) Negative Words (Mean 12891.65, SEM 38.09)	3.098	0.008
Post-Treatment, Old Words	Positive Words faster than Negative Words	Positive Words (Mean 1213.85, SEM 36.80) Negative Words (Mean 12891.65, SEM 38.09)	3.048	0.009
Post-Treatment, New Words	Neutral Words faster than Negative Words	Neutral Words (Mean 927.43, SEM 25.09) Negative Words (Mean 1001.85, SEM 25.22)	3.856	0.001
Post-Treatment, New Words	Neutral Words faster than Positive Words	Neutral Words (Mean 927.43, SEM 25.09) Positive Words (Mean 1016.75, SEM 32.47)	5.222	<0.001

3.3.4.2.1 Summary of Word Recognition Old/New Analyses

3.3.4.2.2 Summary of Old/New Accuracy

See Section 3.3.4.1

There were no effects of treatment on this data. Greater accuracy was seen for all old words at baseline compared to post-treatment. Negatively and positively valenced new words were more accurate at post-treatment compared to baseline.

3.3.4.2.3 Summary of Old/New Response Reaction Time

See Section 3.3.4.2

Response reaction times were faster at post-treatment for both old and new words. Significantly different response times were seen for neutral words, except for those in the post-treatment, old words grouping. For new words, at both baseline and post-treatment there were faster responses made to neutral words relative to both negative and positive words which may be an indication of the more global processing of emotionality slowing response speeds. No effects of treatment were found in this analysis.

3.3.5 Word Recognition Remember/Know

Prior to the main analysis, one-way ((7) Treatment) ANOVAs conducted on baseline scores found that there were no differences in baseline scores across the treatment groups for any of the word recognition Remember/Know measures.

See Appendix 3.5 for the means and SEMs for the recognition type analysis of subjective recollection or familiarity judgements. Significant effects and interactions are indicated.

A four-way mixed factorial ANOVA was conducted on participants subjective recollection (remember) or familiarity (know) judgements of responses to correctly recognised 'old' previously studied words. The primary four-way treatment x time x recognition type x valence interaction was not significant ($F(12,156) = 1.193$, $p = .293$, $r = 0.13$). Significant main effects and interactions are shown in Table 3.14 below. Only significant higher order interactions are reported in the text.

Table 3.14 Word recognition Recollection/Familiarity ANOVA. F values, degrees of freedom, significance levels and effect sizes for interactions and main effects are shown.

Main Effects/ Interactions	Df	F	p value	r
Time x Recognition Type x Valence	(2,156)	3.705	0.027	0.09
Time x Valence x Treatment	(2,156)	2.158	0.016	0.15
Recognition Type x Valence	(2,156)	5.005	0.008	0.12
Time x Recognition Type	(1,78)	7.474	0.008	0.05
Valence	(2,156)	5.352	0.006	0.11
Time	(1,78)	7.470	0.008	0.05

There was a significant time x recognition type x valence interaction($F(2,156) = 3.705$, $p = 027$, $r = 0.09$) (see Table 3.14 above and Table 3.15 below for interaction means and SEMs). Significant pairwise comparisons are summarised in Table 3.16 and Figure 3.7 below.

Interaction effects of time showed greater percentages of correct recollection judgements of negative words were made at baseline compared to post-treatment. This was reversed for positive words which evoked more correct recollection judgements at post-treatment relative to baseline.

Effects of recognition type on the interaction revealed that at post-treatment and for correctly recognised negative words, there were more familiarity judgements made compared to recollection judgements. Also, at post-treatment for correctly recognised neutral words and positive words, there were more recollection judgements made compared to familiarity judgements.

Valence effects on the interaction showed that at post-treatment, more recollection judgements were made for positive words compared to negative words. Also, at post-treatment more familiarity judgements were made for negative words compared to both neutral and positive words.

Table 3.15 Word recognition Recollection/Familiarity. Means and SEMs depicting the 3 way time x recognition type x valence interaction.

Time	Recognition Type	Valence	Mean	±	SEM
Baseline	Recollection	Negative	33.50	±	1.02
		Neutral	32.68	±	1.03
		Positive	31.33	±	1.22
	Familiarity	Negative	35.81	±	2.12
		Neutral	29.74	±	2.18
		Positive	33.12	±	1.88
Post Treatment	Recollection	Negative	30.66	±	1.02
		Neutral	31.12	±	1.20
		Positive	35.73	±	1.19
	Familiarity	Negative	36.93	±	2.36
		Neutral	25.46	±	2.24
		Positive	26.51	±	2.30

Figure 3.7 Word recognition Recollection/Familiarity. Pairwise comparisons from the3 way time x recognition type x valence interaction. Figure key shows pairwise comparisons and significance levels. *(*p < .05,p<.005, ***p<.001)* Bars show standard error.**

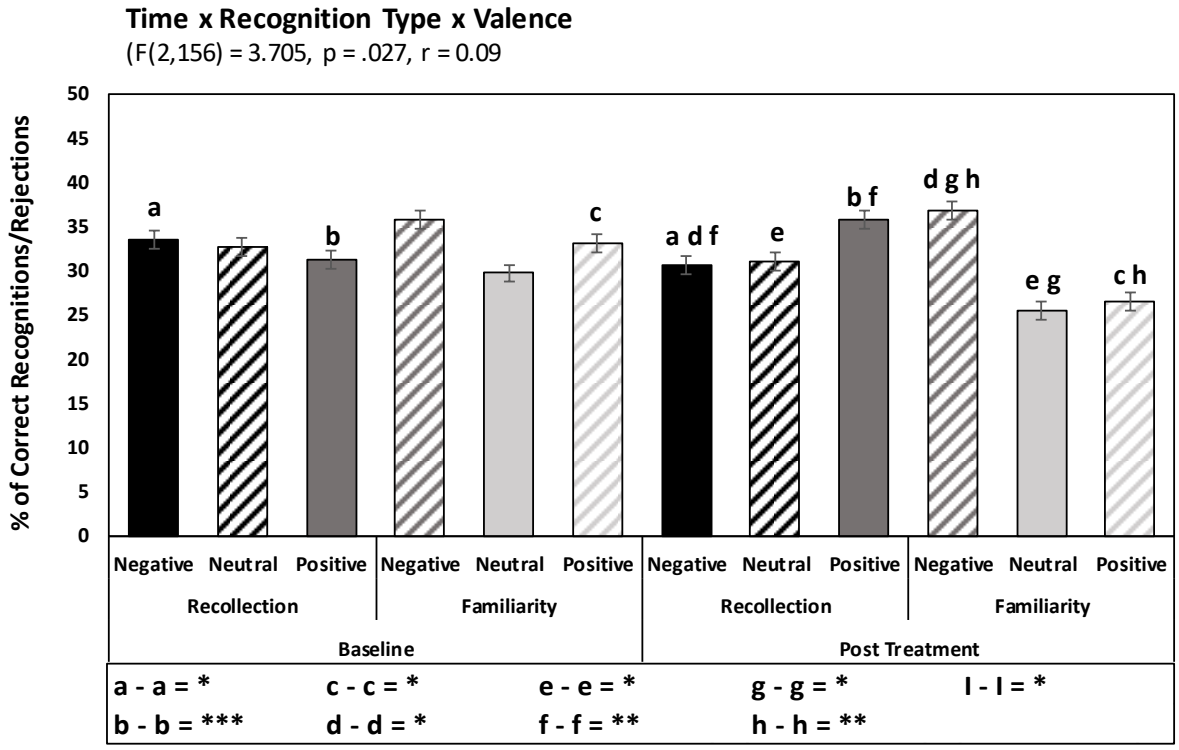


Table 3.16 Word recognition Recollection/Familiarity. Significant pairwise comparisons for the three-way time x recognition type x valence interaction. Group, pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Group	Pairwise Differences in Accuracy	Mean(SEM)	t(78)=	p Value
Recollection, Negative	Baseline > Post-Treatment	Baseline (Mean 33.50, SEM 1.20) Post-Treatment (Mean 30.36, SEM 1.02)	2.776	0.007
Recollection, Positive	Post-Treatment > Baseline	Baseline (Mean 31.33, SEM 1.22) Post-Treatment (Mean 35.73, SEM 11.85)	4.384	<0.001
Familiarity, Positive	Baseline > Post-Treatment	Baseline (Mean 33.12, SEM 1.88) Post-Treatment (Mean 26.51, SEM 2.30)	2.086	0.04
Post-Treatment, Negative	Familiarity > Recollection	Recollection (Mean 30.66, SEM 1.02) Familiarity (Mean 36.93, SEM 2.36)	2.444	0.017
Post-Treatment, Neutral	Recollection > Familiarity	Recollection (Mean 31.12, SEM 1.20) Familiarity (Mean 25.46, SEM 2.24)	2.056	0.043
Post-Treatment, Positive	Recollection > Familiarity	Recollection (Mean 35.73, SEM 1.19) Familiarity (Mean 26.51, SEM 2.30)	3.283	0.002
Post-Treatment, Recollection	Positive Words > Negative Words	Positive Words (Mean 33.73, SEM 1.19) Negative Words (Mean 30.66, SEM 1.02)	3.277	0.005
Post-Treatment, Familiarity	Negative Words > Neutral Words	Neutral Words (Mean 25.48, SEM 2.24) Negative Words (Mean 36.93, SEM 2.36)	3.345	0.004
Post-Treatment, Familiarity	Negative Words > Positive Words	Negative Words (Mean 36.93, SEM 2.36) Positive Words (Mean 26.51, SEM 2.30)	2.982	0.011

There was a significant three-way time x valence x treatment interaction ($F(2,156) = 2.158$, $p = .016$, $r = 0.15$) (see Table 3.14 above and Table 3.17 below for interaction means and SEMs) for the word recognition recollection/familiarity analysis. Significant pairwise comparisons are summarised in Table 3.18 below. There were no treatment effects on the interaction.

Interaction effects of time revealed that following the lemon juice/saccharin treatment there were more correct recognitions of neutral words at baseline compared to post-treatment; following the lemon juice/aspartame treatment there were more correct recognitions of negative words at baseline compared to post-treatment.

The effect of valence on the interaction showed that at post-treatment, following both the Robinsons/saccharin and lemon juice/saccharin treatments there were more correct recognitions to negative words compared to neutral words. At baseline following the lemon juice/aspartame treatment, there were more correct recognitions to negative words compared to both neutral and positive words.

Table 3.17 Word recognition Recollection/Familiarity means and SEMs depicting the time x valence x treatment interaction.

Treatment	Time	Valence	Mean	±	SEM
Robinson's Sugar Free & Glucose	Baseline	Negative	33.74	±	3.03
		Neutral	26.53	±	3.15
		Positive	30.64	±	2.89
	Post-Treatment	Negative	34.69	±	3.48
		Neutral	29.92	±	3.12
		Positive	25.89	±	3.19
Robinson's Sugar Free & Saccharin	Baseline	Negative	32.91	±	3.35
		Neutral	30.85	±	3.48
		Positive	36.24	±	3.19
	Post-Treatment	Negative	41.24	±	3.85
		Neutral	28.13	±	3.44
		Positive	30.63	±	3.53
Robinson's Sugar Free & Aspartame	Baseline	Negative	36.07	±	2.31
		Neutral	32.56	±	2.40
		Positive	31.26	±	2.20
	Post-Treatment	Negative	30.99	±	2.65
		Neutral	29.54	±	2.37
		Positive	36.84	±	2.43
Lemon Juice & Glucose	Baseline	Negative	33.57	±	2.90
		Neutral	34.67	±	3.02
		Positive	31.76	±	2.77
	Post-Treatment	Negative	31.20	±	3.34
		Neutral	27.92	±	2.98
		Positive	32.55	±	3.06
Lemon Juice & Saccharin	Baseline	Negative	31.87	±	3.18
		Neutral	33.52	±	3.30
		Positive	34.61	±	3.03
	Post-Treatment	Negative	36.16	±	3.65
		Neutral	22.05	±	3.27
		Positive	31.80	±	3.35
Lemon Juice & Aspartame	Baseline	Negative	42.41	±	2.90
		Neutral	27.53	±	3.02
		Positive	30.06	±	2.77
	Post-Treatment	Negative	28.14	±	3.34
		Neutral	30.41	±	2.98
		Positive	28.51	±	3.06
Water	Baseline	Negative	32.01	±	2.90
		Neutral	32.81	±	3.02
		Positive	31.01	±	2.77
	Post-Treatment	Negative	34.15	±	3.34
		Neutral	30.05	±	2.98
		Positive	31.64	±	3.06

Table 3.18 Word recognition Recollection/Familiarity. Significant pairwise comparisons for the three-way time x valence x treatment interaction on Word Recognition Accuracy. Group, pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Group	Pairwise Differences	Mean(SEM)	t(77)=	p Value
Lemon Juice/Saccharin, Neutral Words	Baseline > Post-Treatment	Baseline (Mean 33.52, SEM 3.30) Post-Treatment (Mean 22.05, SEM 3.27)	2.919	0.005
Lemon Juice/Aspartame, Negative Words	Baseline > Post-Treatment	Baseline (Mean 42.41, SEM 2.90) Post-Treatment (Mean 28.14, SEM 3.34)	3.530	0.001
Robinson's/Saccharin, Post-Treatment	Negative Words > Neutral Words	Neutral Words (Mean 28.13, SEM 3.44) Negative Words (Mean 41.24, SEM 3.85)	2.460	0.048
Lemon Juice/Saccharin, Post-Treatment	Negative Words > Neutral Words	Neutral Words (Mean 22.05, SEM 3.27) Negative Words (Mean 36.16, SEM 3.65)	2.790	0.011
Lemon Juice/Aspartame, Baseline	Negative Words > Neutral Words	Neutral Words (Mean 27.53, SEM 3.02) Negative Words (Mean 42.41, SEM 2.90)	2.947	0.13
Lemon Juice/Aspartame, Baseline	Negative Words > Positive Words	Positive Words (Mean 30.05, SEM 2.77) Negative Words (Mean 42.41, SEM 2.90)	2.947	0.026

3.3.5.1.1 Summary of Word Recognition Recollection/Familiarity

See Section 3.3.4.2.1

There were no effects of treatment on the subjective recognition judgements made for correctly recognised old words. At post-treatment more recollection compared to familiarity judgements were made for neutral and positive words whereas for negative words there were more familiarity judgements. This may imply greater memory strength for positive and neutral recognitions.

3.3.6 Picture Recognition

3.3.6.1 Picture Recognition Old/New Accuracy

Prior to the main analysis, one-way ((7) Treatment) ANOVAs conducted on baseline scores found that there were no differences in baseline scores across the treatment groups for any of the picture recognition Old/New accuracy measures.

See Appendix 3.6 for the means and SEMs for the Picture Recognition Old/New Accuracy analysis. Significant effects and interactions are indicated.

The primary four-way treatment x time x picture type x valence interaction was not significant (F(12,164) = 1.273, p = .239, r = 0.06). Significant main effects and interactions are shown in **Table 3.19** below. Only significant higher order interactions are reported in the text.

Table 3.19 Picture recognition accuracy ANOVA. F values, degrees of freedom, significance levels and effect sizes for interactions and main effects are shown.

Main Effects/ Interactions	Df	F	p value	r
Time x Picture Type x Valence	(2,164)	3.078	0.049	0.04
Time x Valence	(2,164)	5.874	0.003	0.05
Time x Picture Type	(1,82)	13.577	<0.001	0.07
Valence	(2,164)	5.597	0.004	0.05
Picture Type	(1,82)	75.208	<0.001	0.28
Time	(1,82)	765.416	<0.001	0.71

The three-way time x picture type x valence interaction was significant (F(2,164) = 3.078, p = .049, r= 0.04) (see Table 3.19 above and Table 3.20 below for interaction means and SEMs). Significant pairwise comparisons can be seen in Table 3.21 and Figure 3.8

Effects of time on the interaction showed that there were more correct picture recognitions (i.e., correct recognitions of old, previously seen pictures, and correct rejections of new, not previously seen pictures) of all three valences post-treatment relative to baseline.

Interaction effects of picture type revealed that there were more correct (rejections) responses to new pictures at both baseline and at post-treatment across all three valences, compared to correct (recognition) responses of old pictures.

Valence effects on the interaction showed that at baseline there were more correct recognitions of old neutral pictures compared to old negative pictures. At post-treatment there were more correct rejections of both new negative and new neutral pictures than for new positive pictures.

Table 3.20 Picture recognition Old/New Accuracy. Means and SEMs depicting the time x picture type x valence interaction.

Time	Picture Type	Valence	Mean	±	SEM
Baseline	Old Picture	Negative	46.877	±	1.227
		Neutral	52.374	±	1.368
		Positive	48.854	±	1.844
	New Picture	Negative	57.32	±	1.318
		Neutral	58.768	±	1.243
		Positive	60.999	±	1.402
Post Treatment	Old Picture	Negative	77.784	±	2.064
		Neutral	79.989	±	2.18
		Positive	77.254	±	2.052
	New Picture	Negative	95.584	±	0.926
		Neutral	95.48	±	0.767
		Positive	90.846	±	1.174

Figure 3.8 Picture Recognition Old/New Accuracy. Pairwise comparisons from the3 way time x picture type x valence interaction. Figure key shows pairwise comparisons and significance levels. *(*p < .05,p<.005, ***p<.001)* Bars show standard error.**

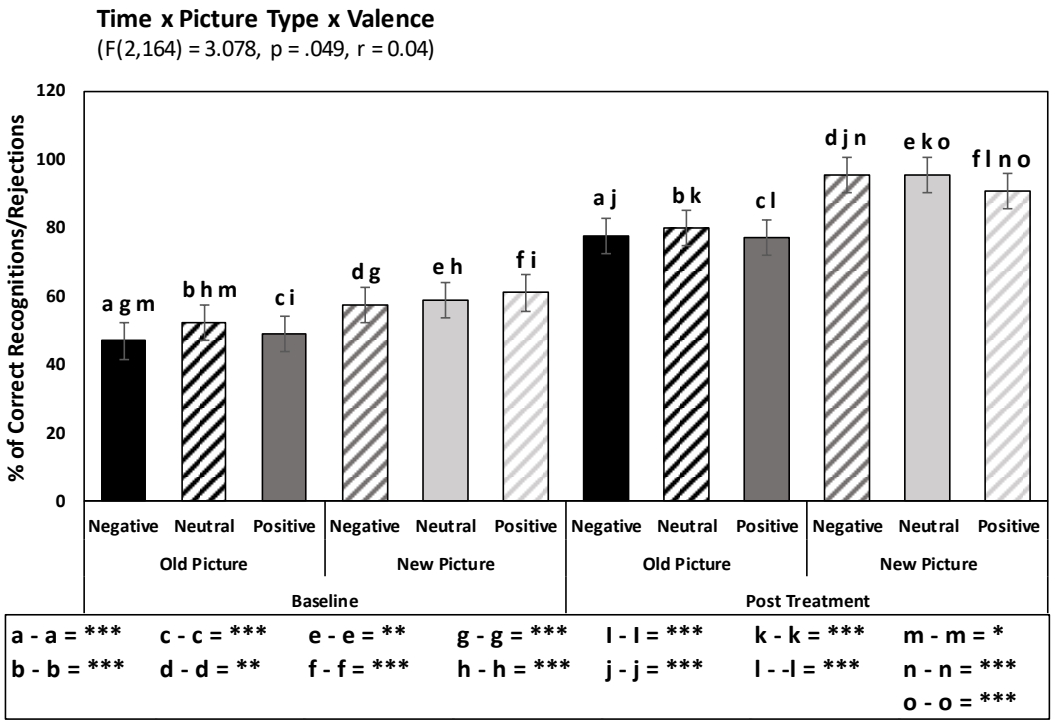


Table 3.21 Picture recognition Old/New Accuracy. Significant pairwise comparisons for the three-way time x picture type x valence interaction. Group, pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Group	Pairwise Differences in Accuracy	Mean(SEM)	t(82)=	p Value
Old Pictures, Negative	Post-Treatment > Baseline	Baseline (Mean 46.88, SEM 1.23) Post-Treatment (Mean 77.78, SEM 2.06)	13.182	<0.001
Old Pictures, Neutral	Post-Treatment > Baseline	Baseline (Mean 52.37, SEM 1.37) Post-Treatment (Mean 79.99, SEM 2.18)	12.621	<0.001
Old Pictures, Positive	Post-Treatment > Baseline	Baseline (Mean 48.85, SEM 1.84) Post-Treatment (Mean 77.25, SEM 2.05)	13.290	<0.001
New Pictures, Negative	Post-Treatment > Baseline	Baseline (Mean 57.32, SEM 1.32) Post-Treatment (Mean 95.58, SEM 0.26)	24.202	0.001
New Pictures, Neutral	Post-Treatment > Baseline	Baseline (Mean 58.77, SEM 1.24) Post-Treatment (Mean 95.48, SEM 0.77)	24.639	0.001
New Pictures, Positive	Post-Treatment > Baseline	Baseline (Mean 61.00, SEM 1.40) Post-Treatment (Mean 90.85, SEM 1.17)	16.721	<0.001
Baseline, Negative	New Pictures > Old Pictures	Old Pictures (Mean 46.88, SEM 1.23) New Pictures (Mean 57.32, SEM 1.32)	5.450	<0.001
Baseline, Neutral	New Pictures > Old Pictures	Old Pictures (Mean 52.37, SEM 1.37) New Pictures (Mean 58.77, SEM 1.24	3.348	<0.001
Baseline, Positive	New Pictures > Old Pictures	Old Pictures (Mean 48.85, SEM 1.84) New Pictures (Mean 61.00, SEM 1.40)	4.905	<0.001
Post-Treatment, Negative	New Pictures > Old Pictures	Old Pictures (Mean 77.78, SEM 2.06) New Pictures (Mean 95.58, SEM 0.93)	8.357	<0.001
Post-Treatment, Neutral	New Pictures > Old Pictures	Old Pictures (Mean 79.99, SEM 2.18) New Pictures (Mean 95.48, SEM 0.77)	7.256	<0.001
Post-Treatment, Positive	New Pictures > Old Pictures	Old Pictures (Mean 77.25, SEM 2.05) New Pictures (Mean 90.85, SEM 1.17)	5.701	<0.001
Baseline, Old Pictures	Neutral Pictures > Negative Pictures	Neutral Pictures (Mean 52.37, SEM 1.37) Negative Pictures (Mean 46.88, SEM 1.23)	3.161	0.007
Post-Treatment, New Pictures	Negative Pictures > Positive Pictures	Negative Pictures (Mean 95.58, SEM 0.93) Positive Pictures (Mean 90.85, SEM 1.17)	4.412	<0.001
Post-Treatment, New Pictures	Neutral Pictures > Positive Pictures	Neutral Pictures (Mean 95.48, SEM 0.77) Positive Pictures (Mean 90.85, SEM 1.17)	4.291	<0.001

3.3.6.1.1 Summary of Picture Recognition Old/New Analyses

See Section 3.3.5.1.1

There were no treatment effects for the picture recognition task. Recognitions were globally more accurate at post-treatment compared to baseline. In terms of valence, at baseline there were more correct recognitions of old neutral compared to old negative pictures. At post-treatment more new negative pictures were correctly rejected than new neutral pictures. No evidence is seen here that manipulating the emotionality of the stimuli has any enhancement effects.

3.3.7 Flanker Task

3.3.7.1 Accuracy

Prior to the main analysis, one-way ((7) Treatment) ANOVAs conducted on baseline scores found that there were no differences in baseline scores across the treatment groups for any of the Flanker task accuracy measures.

See Appendix 3.7 for the means and SEMs for the Flanker task accuracy analysis. Significant effects and interactions are indicated.

The accuracy analysis of Flanker task data showed that the primary four-way time x treatment x congruency x direction interaction was not significant ($F(18,255) = 0.545$, $p = .423$, $r = 0.02$). See **Table 3.22** below for significant main effects and interactions. Only significant higher order interactions are reported in the text.

Table 3.22 Flanker task accuracy ANOVA. F values, degrees of freedom, significance levels and effect sizes for interactions and main effects are shown.

Main Effects/ Interactions	Df	F	p value	r
Time x Direction	(1,85)	5.199	0.025	0.02
Congruency	(3,255)	31.920	<0.001	0.41

There was a significant time x direction interaction ($F(1,85) = 5.199$, $p = .025$, $r = 0.02$) (see **Table 3.22** above and **Table 3.23** below for interaction means and SEMs). Pairwise comparisons revealed a directional effect on the interaction showing that at post-treatment accuracy was greater for left compared to right arrow flankers ($t(85) = 2.970$, $p = 0.004$). There were no effects of time on the interaction.

Table 3.23 Flanker Task accuracy analysis means and SEMs depicting the 2 way time x direction interaction.

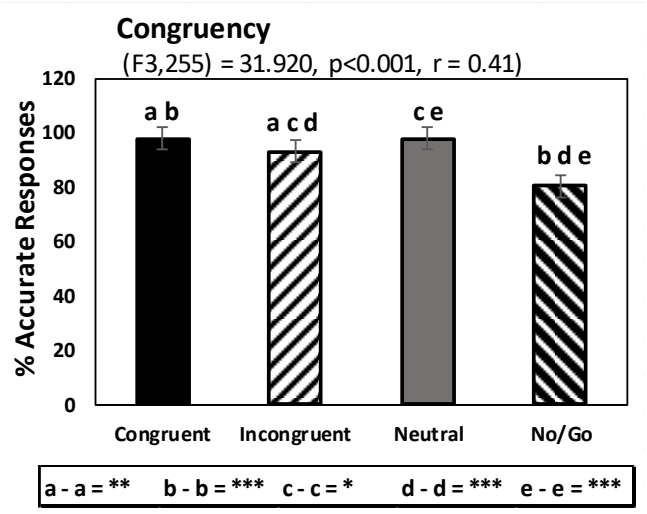
Time	Direction	Mean	±	SEM
Baseline	Left	91.944	±	1.067
	Right	92.361	±	0.991
Post Treatment	Left	93.008	±	0.921
	Right	92.104	±	0.999

For the main effect of congruency (F(3,255) = 31.920, p<.001, r = 0.41) (see **Table 3.22** above) significant pairwise comparisons (see **Table 3.24** and **Figure 3.9** below) revealed that congruent Flanker responses were significantly more accurate than incongruent and NoGo responses. Incongruent responses were significantly less accurate than neutral responses but more accurate than No/Go responses. Neutral responses were more accurate than both incongruent and NoGo responses. In terms of mean accuracy, congruent responses were greater and NoGo responses were least accurate.

Table 3.24 Flanker Task Accuracy. Significant pairwise comparisons for the main effect of congruency. Group, pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Group	Pairwise Differences in Accuracy	Mean(SEM)	t(83)=	p Value
Congruent	Congruent > Incongruent	Congruent (Mean 90.94, SEM 0.46)	3.510	0.004
		Incongruent (Mean 93.11, SEM 1.58)		
Congruent	Congruent > No/Go	Congruent (Mean 90.94, SEM 0.46)	6.770	<0.001
		No/Go (Mean 80.59, SEM 2.63)		
Incongruent	Neutral > Incongruent	Neutral (Mean 97.78, SEM 0.40)	3.335	0.008
		Incongruent (Mean 93.11, SEM 1.58)		
Incongruent	Incongruent > No/Go	Incongruent (Mean 93.11, SEM 1.58)	4.416	<0.001
		No/Go (Mean 80.59, SEM 2.63)		
Neutral	Neutral > No/Go	Neutral (Mean 97.78, SEM 0.40)	2.556	<0.001
		No/Go (Mean 80.59, SEM 2.63)		

Figure 3.9 Flanker Task Accuracy. Pairwise comparison from the main effect of congruency. Figure key shows pairwise comparisons and significance levels. (*p<.05,p < .005, ***<.001) Bars show standard error.**



3.3.7.2 Response Reaction Time

Prior to the main analysis, one-way ((7) Treatment) ANOVAs conducted on baseline scores found that there were no differences in baseline scores across the treatment groups for any of the Flanker task response reaction time measures.

See Appendix 3.8 for the means and SEMs of the Flanker task response reaction time analysis. Significant effects and interactions are indicated.

The response reaction time analysis of Flanker task data showed that the primary four-way time x treatment x congruency x direction interaction was not significant ($F(12,166) = 0.547$, $p = .881$, $r = 0.02$). See Table 3.25 below for significant main effects and interactions. Only significant higher order interactions are reported in the text.

Table 3.25 Flanker task response reaction time ANOVA. F values, degrees of freedom, significance levels and effect sizes for interactions and main effects are shown.

Main Effects/ Interactions	Df	F	p value	r
Time x Direction	(1,83)	4.609	0.035	0.02
Time	(1,83)	41.735	<0.001	0.17
Congruency	(1.42,117.84)	153.500	<0.001	0.36
Direction	(1,83)	6.339	0.014	0.04

There was a significant time x direction interaction ($F(1,83) = 4.609$, $p = .035$, $r = 0.02$) (see Table 3.25 above and Table 3.26 below for interaction means and SEMs). Pairwise comparisons (see Table 3.27 below) revealed an effect of time on the interaction showing that at post-treatment right flanker responses were faster than left arrow flankers. Interaction effects of direction showed that right arrow flanker responses were faster than left responses at post-treatment.

Table 3.26 Flanker Task Response Reaction Time. Means and SEMs depicting the 2 way time x direction interaction.

Time	Direction	Mean	±	SEM
Baseline	Left	539.24	±	7.01
	Right	535.84	±	6.76
Post Treatment	Left	517.45	±	6.81
	Right	508.23	±	6.05

Table 3.27 Flanker Task Response Reaction Time. Significant pairwise comparisons for the 2 way time x direction interaction. Group, pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Group	Pairwise Differences in Response Speed	Mean(SEM)	t(83)=	p Value
Left Direction	Post-Treatment faster than Baseline	Baseline (Mean 539.24, SEM 7.01)	5.527	<0.001
		Post-Treatment (Mean 517.45, SEM 6.81)		
Right Direction	Post-Treatment faster than Baseline	Baseline (Mean 535.24, SEM 6.76)	6.626	<0.001
		Post-Treatment (Mean 508.23, SEM 6.05)		
Post-Treatment	Right Responses faster than Left Responses	Left (Mean 517.45, SEM 6.81)	3.492	0.001
		Right (Mean 508.23, SEM 6.05)		

For the main effect of congruency ($F(1.42,117.84) = 153.500$, $p<.001$, $r = 0.36$) (see Table 3.25 above) significant pairwise comparisons (see Table 3.28 below) revealed that congruent Flanker responses were significantly faster than incongruent and neutral responses. Neutral responses were also significantly faster than incongruent responses.

Table 3.28 Flanker Task Response Reaction Time. Significant pairwise comparisons for the main effect of congruency. Group, pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Group	Pairwise Differences in Response Speed	Mean(SEM)	t(82)=	p Value
Congruent	Congruent faster than Incongruent	Congruent (Mean 503.08, SEM 6.03	13.929	<0.001
		Incongruent (Mean 562.32, SEM 7.18)		
Congruent	Congruent faster than Neutral	Congruent (Mean 503.08, SEM 6.03	3.193	0.006
		Neutral (Mean510.17, SEM 6.48)		
Incongruent	Neutral faster than Incongruent	Neutral (Mean510.17, SEM 6.48)	12.327	<0.001
		Incongruent (Mean 562.32, SEM 7.18)		

3.3.7.2.1 Summary of Flanker Task

The Go/No Go inhibition paradigm used here demonstrated that at post-treatments accuracy was greater for left compared to right arrow Flankers. Additionally, accuracy was indeed diminished for No Go responses compared to congruent, incongruent, and neutral Flankers. In terms of response reaction times, faster responses were seen at post-treatment for left and right arrow Flankers with faster right compared to left arrow responses. Congruent Flanker responses were faster than responses to both incongruent and neutral Flanker arrays. There were no treatment effects seen for the Flanker task.

3.4 Exploratory Word Recognition Analyses

3.4.1 Overall Memory Performance for Individual Treatments

The primary aim of this study was to ascertain the efficacy of treatments to be used for the remaining studies contained in this thesis. No effects of glucose were observed in the analyses conducted in this chapter. However, previous research has found effects of glucose on accuracy and response reaction speeds. It may be considered a limitation of this study that the complex design may have been masking potential effects. To explore this possibility 'overall correct' data was analysed as 'split file' data, with separate outcomes for individual treatments, via a two-way Treatment (7) x Time (2) mixed-measures ANOVA with the percentage of correct responses overall acting as the dependent variable. None of the primary time x treatment interactions were significant.
Overall Memory Performance for Selected Treatments

A further exploratory analysis was also conducted using the treatment combinations which have been selected for the remaining studies, as such, Robinsons/Glucose and Robinsons/Saccharin. A two-way Treatment (2) x Time (2) mixed-measures ANOVA was conducted to assess any differences in overall correct responses. The primary two-way time x treatment ANOVA interaction was not significant ($F(1,18) = 3.307$, $p = 0.086$, $r = 0.18$).

3.4.1.1 Summary of Exploratory Word Recognition Results

These further analyses were based on the postulation that glucose effects may have been masked by the complexity of the design, however no effects of glucose were found for the word recognition data within these exploratory analyses.

3.5 Discussion

3.5.1 Summary of Main Findings

The primary aim of this chapter was to further investigate anomalies in the glucose enhancement literature. The findings of chapter 2 suggested that some of the ingredients commonly used in the preparation of experimental and placebo treatments may not, as previously assumed, be cognitively

inert. This chapter further investigated these inconsistencies by exploring the effects of commonly used treatment combinations. Any treatment effects which could not be attributed to glucose would indicate that treatment ingredients, such as non-nutritive sweeteners or flavour masks, were not cognitively inert. Any such findings would signify that these treatment combinations were unsuitable for use in future chapters of this thesis. In contrast with chapter 2, there was no evidence in this chapter to suggest that any of the non-nutritive sweeteners or flavour masks were having active effects on the cognitive tasks when used in the combinations utilised here.

This chapter also sought to investigate whether the impact of the emotionality of stimuli would support previous research which suggested that glucose enhancement of emotional stimuli is facilitated by (potentially) elevating blood glucose levels (Parent et al., 1999; Scholey et al., 2006; (Blake et al., 2001). If this effect is present, a more global availability of glucose would enhance both recollection and familiarity. If increased circulatory blood glucose was preferentially targeting the hippocampus, then domain related enhancement would enhance recollection only. No evidence was found from the subjective 'Recollection/Familiarity' data to support this, but the old/new data revealed that there were more correct rejections of positive and negative distractors at post-treatment, which may offer partial support for the efficacy of facilitation being driven by an emotion linked increase in blood glucose levels.

The impact of ingested glucose on sustained attention and inhibition during the Flanker task was also investigated, specifically whether glucose modulated the conflicting Go/NoGo responses. Again, as there were no treatment effects, no evidence was found in this chapter to support glucose enhancement of attentional resources.

3.5.1.1 Treatment Combination Effects

This chapter aimed to advance the findings of chapter 2 with a view to selecting which treatment ingredients would be used for the remaining studies in this thesis. However, no treatment effects were found in this chapter, for any of the cognitive tasks performed by participants. As such, no definitive choice could be made based on the efficacy of the combined treatment ingredients. Based on chapter 2, some elements of cognitive performance (Stroop RT and choice reaction accuracy) in the lemon juice condition were significantly different to the water control. The orange juice condition only indicated cognitive changes in the serial 7's task. As such, orange juice was selected as the flavour mask due to fewer indicated cognitive effects.. . No clear effects of non-nutritive sweeteners

were observed for aspartame or saccharin. As such, saccharin was utilised on the basis of aspartame detrimental impairments reported in the literature (Linseth, et al., 2014; Konen, et al., 2000).

Findings concerned with ingested glucose and glucoregulatory control were more consistent from the body of research which commonly used a 25 gm glucose experimental dose, or 5 x saccharin based non-nutritive 'Mini-Sweeteners' (www.Hermesetas.com) placebo dose administered via a 200ml drink containing Robinsons Sugar Free Orange Cordial (20 mls) as a flavour mask. These treatment drinks have been shown to be matched for sweetness and oral texture and used for similar studies in the literature (Ford, Scholey, Ayre, & Wesnes, 2002; Kennedy & Scholey, 2000; Scholey, MacPherson, Sünram-Lea, Elliott, Stough, & Kennedy, 2013; Scholey, et al., 2009; Scholey & Fowles, 2002).

3.5.1.2 Word Recognition

This chapter aimed to investigate whether task demand is an influential factor in the glucose enhancement of recognition memory. It was proposed that, (a) if glucose enhancement was subserved by increased cognitive demand, a more global facilitation would enhance both recollection and familiarity recognition processes or (b) if glucose was domain specific and preferentially targeting hippocampal memory functions, then enhancement would be observed for recollective recognitions but not for familiarity recognition. On the other hand, there is also the possibility that glucose facilitation is driven by both of these concepts. There were no glucose effects on any aspect of word recognition. This supports the Scholey et al. (2013) study which did not observe any effects of glucose on recollection and familiarity.

The word recognition accuracy time x word type x valence interaction did not offer any conclusive evidence in terms of the demand hypothesis. In terms of response reaction times, a time x word type x valence interaction revealed faster responses for new neutral words relative to new negative (but not positive) words at baseline. There was a similar pattern at post treatment but here neutral responses were faster than both new negative and new positive words. This finding may identify slower processing of emotionally valenced stimuli which may indicate that more global processing is involved.

For the analysis of subjective 'Remember/Know' data there was no conclusive evidence regarding recollection judgements and familiarity judgements from the time x recognition type x valence

interaction. This identified that for correctly recognised negative words there were more familiarity judgements made than recollection judgements at post-treatment. However, this effect was not consistent and was reversed for positive and neutral words, where more recollection than familiarity judgements were made. There was also a time x valence x treatment interaction, but again there were no significant effects of treatment and comparisons between valences were inconclusive in terms of the research question.

Considering these outcomes alongside the Scholey et al. (2006) study, which also manipulated the emotionality of the stimuli, this chapter offers partial support for their finding with no memorial advantage being observed from this manipulation. Differentially from the Scholey et al.'s study, no measures of circulatory blood glucose were taken here, although in some conditions a glucose dose was administered. However, Scholey et al. (2006) did find that blood glucose levels were elevated by exposure to emotional stimuli. This could be due to increased processing demands of this stimuli type requiring increased glucose provision in the brain. Or conversely, this may be a peripheral effect with the emotional stimuli triggering the sympathetic adrenal medullary (SAM) which elevates heart rate and blood glucose levels. Due to this, regardless of which mechanism, increased exogeneous glucose supplementation may facilitate cognitive processing of these stimuli. This potentially implies that increasing blood glucose levels via a glucose dose impacts this mechanism and/or may have an enhancement effect. Thus, positing the question, in what way does ingested glucose impact cognition in this scenario? However, this chapter did observe slower response speeds for new negative and new positive words in comparison to new neutral words at both baseline and post-treatment which may also offer some support for more global processing of emotional stimuli.

3.5.1.3 Exploratory Word Recognition Analyses.

No glucose effects were observed in either of the analyses which were conducted to explore treatment differences on overall memory performance. Scholey et al.'s (2013) study reported overall memory performance was lessened rather than enhanced following glucose. However, Scholey et al. used a sensorimotor task during encoding to create a high demand, with participants not performing the task during 'low demand' encoding. For the high demand condition, it was found that glucose enhanced overall word recall performance. It may be that the demand characteristics of the word recognition task used in this chapter were not sufficiently high to enable observable glucose effects, as reported elsewhere. This comparison may demonstrate that the additional attentional resources employed in the processing of emotional stimuli may not be sufficiently demanding to evoke an

enhancement effect. However, it must also be born in mind that this was a small exploratory analysis with a between-groups design.

3.5.1.4 Picture Recognition

No glucose effects were observed for picture recognition. There was a global increase in accuracy at post-treatment compared to baseline, speculatively, as this was observed across all conditions, this may have been a practice effect. At baseline there were more correct recognitions of old neutral compared to old negative pictures with more correct rejections of both new negative and new neutral pictures at post-treatment. No evidence is seen here that manipulating the emotionality of the picture stimuli has any enhancement effects.

3.5.1.5 Flanker Task

No glucose effects were detected by the Flanker task. As would be expected accuracy was greater for congruent, incongruent, and neutral flanker arrays compared to the NoGo condition. Responses to right directional flanker arrays were faster than left pointing arrays at post-treatment and congruent arrays evoked faster responses than did incongruent arrays. There was no evidence from flanker data that glucose or other drink ingredients modulated attentional resources.

3.5.1.6 Limitations

Analysis outcomes demonstrated that there were several indications of practice effects occurring, with performance on the cognitive tasks approaching ceiling at post-tests. This potential practice effect was likely to occur for the post-treatment test battery, consequentially familiarity with the content may have affected performance and responsiveness. However, whilst these practice effects may have been present, participants acted as their own control because they completed both baseline and post-treatment tasks.

The post-treatment task battery followed the baseline testing session with only a fifteen minute break for drink consumption and absorption. As the cognitive tasks took approximately 45 minutes it is possible that participants were more tired and/or bored during the post-treatment session. However, whilst a practice effect may have been present, participants were also exposed to more word lists, which may have impacted on their recall performance for the post-treatment session. These issues will be lessened to some extent for future studies by utilising a within-subjects, so that

during each of the two visits participants will only perform one battery of cognitive tasks, as such reducing the number of word lists.

Although the main objective of this chapter was to determine which drink combinations were suitable for use in the remaining studies in this thesis, it is apparent from the literature that glucoregulatory control appears to be an important element in investigations of glucose administration. Measures of participants circulatory blood glucose and glucoregulatory control would have allowed more in depth comparisons across the glucose literature. To develop this research area further, for the two remaining experimental chapters, participants will undergo an Oral Glucose Tolerance Test (OGTT) which will indicate the efficiency of participants glucoregulatory control.

As this study was conducted as part of students' learning experience it was not ethically appropriate to require that they fast prior to testing. This lack of fasting prior to testing may also be considered as a confound. Although most testing sessions were in the mornings, depending on what they had eaten for breakfast participants blood sugar levels would have been in varying states, and as food intake was not known, this could be a confound. Postprandial blood sugar begins to rise approximately 15 minutes after food and will vary for different foods. As most data was collected in the mornings, some participants will not have eaten breakfast and others may have eaten breakfasts of varying glycaemic loads which will raise postprandial blood glucose levels differentially. In terms of caffeine consumption prior to testing, the mean half-life of caffeine in the plasma of healthy individuals has been found to be approximately five hours (Institute of Medicine (US) Committee on Military Nutrition Research., 2002). As completion of the tasks took place over a two-hour period, any effects of caffeine would have been similar at baseline and post-treatment testing. The effects of caffeine were unknown as it was not known when or if caffeine had been consumed, equally, depending on when they last ate these are all confounding factors. For future studies participants will be asked to undertake a 12 hour overnight fast (with water allowed) to eliminate glycaemic effects prior to testing.

3.5.2 Conclusion

The primary objective of this chapter was to ascertain the efficacy of treatment ingredient choices to be used for future research into the effects of glucose on episodic memory and attention. Whilst no treatment effects were seen throughout the current chapter, based on the outcomes of chapter 2, utilising Robinsons sugar free Orange Cordial as a flavour mask for both the experimental and

placebo treatments is considered to be the best choice. In terms of a non-nutritive sweetener for the placebo treatments, observations by previous research potentially precluded this as a viable drink ingredient. In view of the lack of evidence in the literature to date that saccharin influences cognition, including episodic memory and attentional resources literature, this was selected as the non-nutritive sweetener for the placebo treatments. This combination of treatments has been widely used by laboratories in studies which have reported consistent results (Brown & Riby, 2013; Ford, et al., 2002; Kennedy & Scholey, 2000; Owen et al., 2012; Riby, et al., 2008; Riby et al., 2011; Scholey et al., 2009; Scholey, et al., 2014; Scholey et al., 2013). This treatment formula has been evaluated as having no discernible differences between the oral texture and sweetness/taste between the experimental and the placebo treatments.

The secondary aim of chapter 3 was to explore the effects of ingested glucose on episodic memory, via picture recognition and word recognition tasks, and inhibition, using the Flanker conflict task. In terms of the picture recognition task, there were no glucose effects, nor was there any evidence that manipulating the emotionality of the stimuli had any enhancement effects. Similarly for the Flanker task, there were no effects of glucose and no unexpected outcomes, with greater accuracy and faster responses seen for congruent items and diminished accuracy for the No/Go conflict condition. No glucose effects were observed for any of the word recognition tasks conducted in this chapter. However, there was evidence of more global processing of emotional stimuli with slower response speeds for new negative and new positive words relative to new neutral words. Equally absent was any evidence of glucose effects from the subjective 'Remember/Know' paradigm in which participants judged their correctly remembered responses to previously seen stimuli to be either recollective or familiar.

Ultimately, this lack of glucose effects does not provide support for either the demand or the domain approach to glucose enhancement. An equally persuasive argument is that modest glucose enhancement is present but may be nuanced and not evident in behavioural data. Previous research documented in this chapter has found effects of glucose on memory recall accuracy and response reaction speeds.

Based on the notion that the complexity of the seven x treatment groups between-groups design utilised here may have masked potential effects, analysis of 'overall correct' data, further exploratory analyses (see section 3.4) with separate outcomes for individual treatments was conducted on the

word recognition data. The results reported in this chapter conflict with previous research, tentatively, this may support the theory that glucose enhancement of performance only occurs when there is a high cognitive load. Alternatively, these effects of glucose ingestion may only be seen when individuals are fasted. This outcome may also add credence to the conjecture that the glucose effects may be too subtle to detect in behavioural data.

To further explore the question of whether glucose enhancement is demand or domain determined, or the possibility that glucose effects may be present but too nuanced to be detected in behavioural data, chapter 4 will investigate the effects of glucose on episodic memory at physiological and neurological levels using electrocardiogram (ECG) to monitor heart rate responses and electroencephalogram (EEG) to monitor potential changes in neural activity during word encoding and recognition. Chapter 4 will also address questions raised by the literature concerning glucoregulatory control with participants undergoing an OGTT, which is the gold standard glucose to assess glucose tolerance (see section 1.2.3). This will give measures of individuals' glucoregulatory control which will be utilised to interpret potential effects of glucoregulation and/or ingested glucose effects.

Another line of research which may elucidate the impact of glucoregulatory control concerns the relationship between impaired glucoregulation and the risk for cardiovascular disease (see section 1.4.1). It is suggested that heart rate reserve and recovery rate performance may be predictors of T2DM (Jae et al., 2016), and whilst the mechanisms which subserve this effect are not clear it may be resultant of insulin release being stimulated in response to changes in circulatory blood glucose levels and as such linked to insulin resistance (Panzer et al., 2002). Chapter 4 will investigate the relationship between impaired glucoregulation and heart rate performance by monitoring participants' heart rate in beats per minute whilst cognitive testing is conducted. This approach may reveal glucoregulation differences in HR in young non-diabetic adults and as such, may provide evidence of early markers of potential decrements in glucoregulatory control.

4 The Influence of Ingested Glucose and Glucoregulatory Control on the Neurophysiological and Physiological Correlates of Episodic Memory and Inhibition in Young Non-Diabetic Adults.

4.1 Introduction

The facilitatory effect of elevated blood glucose levels on cognitive functioning is widely reported (for review articles see Messier, 2004; Smith et al., 2011; Stern and Alberini, 2013), with episodic memory specifically seeming to be the cognitive aspect most commonly improved by acute glucose administration. The mechanisms underpinning this effect are unclear, with several competing and valid mechanisms proposed.

Chapter 3 sought to explore two conflicting theories which seek to identify the mechanisms involved in the effects of glucose on episodic memory (see section 1.5.2.6.1.2 for a resume of these theories). The task demand approach proposes that glucose enhancement is subserved by increased cognitive load, suggesting that enhancement effects of glucose are only seen when tasks necessitate a high intensity of cognitive demand (see section 1.5.2.6.1.1). As the opposing theory, the task domain explanation relies on the postulation that the enhancement effect of glucose is subserved by the hippocampus (see 1.5.2.6.1.1) (Riby et al., 2009; Riby, Sünram-Lea, Graham, Cooper, & Gunn, 2008; for a review see Riby, 2012; Scholey et al., 2014; Sünram-Lea, Dewhurst, & Foster, 2008). As in chapter 3, this chapter will explore the debate between the task demand and task domain theories of glucose facilitation. In this chapter these conflicting theories are further explored in terms of the potential effects of glucoregulatory control by assessing participants' glucose tolerance via an OGTT tolerance test (see section 1.2.3 for a detailed description of this test) to split participants into 'better' and 'poorer' glucoregulation groups. Participants followed a 12 hour fast prior to each test visit, and as such, they were assessed in a fasted state following the placebo treatment and in a hyperglycaemic state with blood glucose levels elevated by the experimental treatment.

Understanding the pre-clinical impact of declining glucoregulation may offer the opportunity to identify individuals in the early stages of cognitive decline. Potentially leading to intervention prior to prolonged cumulative damage resulting from insulin neurotoxicity, to which the hippocampus is

vulnerable (Lamport et al., 2014). In a study of 122 healthy non-diabetic young adults Messier et al. (2011) found no behavioural effects of glucose ingestion on cognitive performance but based on evoked measures of fasting glucose levels, the authors found an association between glucose regulation and verbal memory recall. The focus of this chapter will be to further investigate whether primary evidence of cognitive decrement in the early stages of poor glucoregulatory control is observed in healthy non-diabetic young adults. To investigate this further, this chapter will explore the effects of glucose administration on the potential hippocampal underpinning of recollection and familiarity in healthy young adults whilst controlling for levels of glucoregulatory control. Neurophysiological methodology was employed to provide novel insights into the neural correlates of the cognitive processes involved in recognition memory, and potential differences were explored in *a priori* ERP components (see section 1.6.1 for detailed descriptions of these).

To further elucidate whether a performance enhancing effect of glucose administration is the result of glucose targeting hippocampally mediated recollective memory, or whether enhancement is subserved by task demand the remember/know paradigm was employed alongside glucose administration and neuroimaging techniques. A glucose administration study using the remember/know/guess procedure found increased correct recollection, but not familiarity responses, in a population of young healthy adults (age range 18 – 25 years; mean age 20 years) following glucose ingestion compared to placebo offering support for the dual-process model Sünram-Lea et al., (2008). The results of this study suggest that the glucose enhancement effect was targeting hippocampally mediated recollection and as such offers support for glucose enhancement being mediated by domain rather than demand. Conversely, other research which explored whether glucose facilitation was targeting hippocampal memory or whether task demand was a more important determinant of this facilitative effect, employed a secondary hand-movement task during the encoding of verbal stimuli (Scholey, MacPherson, Sünram-Lea, Elliott, Stough, Kennedy, et al., 2013) The authors found that there were no differential effects of glucose for recollection or familiarity responses but suggested that task effort was a more important determinant of glucose facilitation than domain specific hippocampal mediation. Neurological evidence from an EEG study which utilised the remember/know procedure found that two distinct effects were evoked by 'recollection' and 'familiarity' judgements of episodic recall which gave support to the view that these two processes were temporally and topographically different (Rugg et al., 1998). However, compelling evidence from a recent intercranial study found that both recollection and familiarity generated higher frequency activation in the hippocampus which suggests direct involvement of

both processes in the hippocampus (Merkow et al., 2015). Event related potential investigations of glucoregulatory control have revealed prolonged latencies (Hazari et al., 2015) and a correlation between higher blood glucose levels and ERP amplitude and latency in individuals presenting with T2DM (de Freitas Alvarenga et al., 2005).

Glucose enhancement of episodic memory was seen in a further between-groups ERP study which explored the P3 ERP component finding an enhanced late posterior P3 suggesting that glucose enhances recollection (L. A. Brown & Riby, 2013c). Whilst this study did control for glucoregulation, these measures were again based on test-day visit samples, rather than a clinical OGTT, and were included in the analyses as a covariate. Additionally, analysis was only conducted on data from one electrode at the late posterior location (P3) and no analyses of data from the anterior electrodes, which is associated with familiarity, were reported.

The lack of behavioural evidence in Chapter 3 may be explained by the fact that the sample population was a cohort of healthy young adults, and any potential effects may have been too subtle to detect in behavioural data. Research suggests that, in terms of cognitive enhancement, a glucose dose preferentially targets individuals with poorer glucoregulation. Targeting populations such as healthy older adults, for whom a decline in glucoregulatory control is considered a normal function of aging (Riby, 2012), populations with co-morbid poor glucoregulatory control such as patients with Alzheimer's disease, (Manning, et al., 1993), schizophrenia (Stone et al., 2003) and in adults with Down's syndrome (Manning et al., 1998). Cognitive enhancements are generally seen in healthy young adults with healthy levels of glucoregulatory control under circumstances whereby both fasting and high cognitive demand are in place during testing (Scholey, Sunram-Lea, et al., 2009;Scholey, MacPherson, Sünram-Lea, Elliott, Stough, & Kennedy, 2013; S. I. Sünram-Lea et al., 2002) By introducing the fasting element this will make this study more comparable to the existing literature despite being less representative of day-to-day cognitive functioning in this population.

Whilst Chapter 3 did not reveal any significant accuracy effects of valence, the emotional memory enhancement effect has been well documented with both behavioural and neuroimaging research suggesting that emotionally valenced stimuli are preferentially remembered in comparison to neutral stimuli (Griffin, Dewolf, Keinath, Liu, & Reder, 2013; Imbir, Jarymowicz, Spustek, Kuš, & Zygierewicz, 2015; Kensinger & Corkin, 2003; Kissler, Herbert, Peyk, & Junghofer, 2007; Kissler, Herbert, Winkler, & Junghofer, 2009; Maratos, Allan, & Rugg, 2000; Wanat et al., 2009; for reviews see Hamann, 2001;

Smith, Riby, van Eekelen & Foster, 2011). However, for emotionally valenced stimuli, Brandt, Sünram-Lea, & Qualtrough (2006) found that the glucose enhancement effect was not present when the emotional nature of the stimuli already generates a memory advantage. The outcomes of the Brandt et al. study may have been influenced by the between-groups design which does not allow for inter-participant reliability. To address this potential issue this study utilised a mixed factorial design with glucose and placebo conditions being a within-subjects variable, with participants acting as their own control. Brandt et al. did find a negative correlation between blood glucose levels and accuracy for positive stimuli, with lower blood glucose being associated with better performance, but this was based on blood samples taken during test visits rather than pre-test clinical measures of glucoregulatory control. However, in opposition to the emotional enhancement theory, an ERP study (Mao et al., 2015) using the remember/know paradigm alongside emotional images, suggests that emotion-related interference, indicating impaired recollection and familiarity, was seen in response to negative and positive items. Mao et al. suggest that this offers support to the concept of an emotion-induced trade-off. Speculatively this 'trade-off' may be due to emotional stimuli invoking a broader range of attentional resources and as such, increasing cognitive demand. Utilising emotional words and using the 'remember-know' paradigm (Tulving, 1985), chapter 4 further investigates whether emotional valance for verbal stimuli influences memory and, in turn if this effect is modulated by ingested glucose and/or glucoregulatory control. It was expected that glucose would modulate the ERP correlates of memory for emotionally valenced stimuli, which would manifest through the elicitation of differences in mean amplitudes.

Uniquely, neuroimaging studies can collect data during the encoding stage of an experiment, where behavioural data is unobtainable. The current chapter utilised ERPs to examine initial neurological responses to the emotional valence of the stimuli. Research suggests that ERP modulations in response to emotional content can be seen relatively early, with ERP amplitude modulations being visible as early as in the P1 latency window of 100 – 200ms or thereabouts (Hajcak et al., 2012). Emotional content was also processed preferentially during a silent reading task, with differential effects elicited between emotional and neutral stimuli in the 240 – 300 time widow (Kissler et al., 2009). This chapter explores this concept of early emotional effects by recording ERPs during the encoding phase of the recognition memory process. Components for the encoding phase will be P1, N1, P3 and the Late Positive components (see section 1.6.1.1 for descriptions of these).

Neurophysiological data collection and analysis will focus on those ERP components derived from *a priori* assumptions from the recognition memory literature which have indicated sensitivity to the emotional valence of verbal stimuli or the encoding and recognition phases of episodic memory. Investigating recognition memory alongside measures of glucoregulatory control and glucose administration will facilitate a line of research which allows comparisons in terms of which mechanisms are potentially governing the supply of glucose as fuel for the brain whilst also exploring the consequences of low-level dysfunctions in glucoregulation. Conventionally the FN400 component is investigated in the 300 – 500ms time window and is believed to index familiarity at mid-anterior sites. At mid-posterior sites, the Late Positive Component (LPC), in the 400 – 800ms time window, is typically believed to index recollection (for a review see Rugg and Curran, 2007) (Smith et al., 2004).

Sustained attention, the capacity to remain attentive during processing of stimuli presented in a repetitive manner was explored in Chapter 3 via the Flanker conflict task (Eriksen, 1997), see section 1.5.2.3 for details of conflict tasks). Whilst there were significant effects of congruency and response reaction speed, no effects of glucose were observed. In view of research which observed that adults with type 1 diabetes mellitus have been seen to have impaired sustained attention (Van Dijk et al., 2014), with glucose facilitation of cognitive self-control being seen in patients with schizophrenia (Leung et al., 2014), both of which populations have challenged glucoregulation, chapter 4 will explore the possibility that glucoregulatory control may impact attentional resources. It would be expected that performance decrements would be seen for individuals in the 'poorer' glucoregulation group following placebo, with potential glucose enhancement of Flanker performance for poorer, but not better regulators.

Impaired glucose metabolism has been seen to be associated with risk for cardiovascular disease. A twelve-year longevity study of healthy men found that exercise heart rate reserve and recovery rate were predictors of T2DM (Jae et al., 2016). It may therefore be tentatively postulated that early indications of this relationship between heart rate and glucoregulation may be evident. Investigation of glucoregulation differences in heart rate measures, was also addressed by this chapter (see 1.4.1.1.1 for HR methodology). In terms of glucose enhancement of memory, there are mixed findings across the literature concerning physiological responses. Research exploring the relationship between exposure to emotional stimuli and heart rate (HR) found deceleration of heart rate, particularly for stimuli with a negative valence (Bonner & Elliott, Unpublished). A study by Kennedy & Scholey (2000) found an acceleration of heart rate during cognitively demanding tasks following

glucose ingestion, arguing that glucose preferentially targets higher demand tasks. These findings were supported by Ford, Scholey, Ayre, & Wesnes (2002) with emotional material eliciting a decrease in heart rate in the placebo condition but accelerated heart rates for the glucose condition. In terms of the current chapter, it is expected that accelerated heart rate would be seen in response to emotionally valenced words following glucose ingestion. A limitation of the Ford et al study was that heart rate was only assessed by 'snapshot' readings taken alongside blood sampling. A further study investigating the impact of glucose administration on heart rate during challenging cognitive tasks found no effects of glucose on cardiovascular response (Synowski et al., 2013). A study by Elliott & Youll (2013) showed a differential change in heart rate following glucose ingestion, decelerated heart rate was seen when negative words were presented following placebo but not glucose. This was supported by Bonner & Elliott (Unpublished) who also found deceleration of heart rate during exposure to negative words in the placebo condition but not in the glucose condition. To address this gap in the literature, chapter 5 will continuously monitor participants heart rate throughout the encoding phase so that potential physiological effects of first-time exposure to emotional valence in the encoding phases can be observed. By utilising ECG to monitor heart rate during the encoding phase the interaction between glucose ingestion, changes in physiological responses (HR) to neutral and emotionally valenced stimuli will be observed for participants initial exposure to the stimuli.

The primary aim of this chapter is to utilise EEG to investigate the potential for the presence of early, sub-clinical effects of poor glucoregulatory control on the temporal activity associated with episodic memory in non-diabetic healthy young adults. Chapter 3 explored the effects of ingested glucose on the recollection and familiarity components of recognition memory and the main outcome was the absence of treatment effects, specifically from drink combinations containing glucose. This finding does not appear to offer any support for glucose modulating a global enhancement of recognition memory; nor does it offer any support for hippocampal mediation of glucose through glucoregulatory processes and blood glucose levels. However, the lack of evidence for these theoretical approaches posited the question that these effects may be too subtle to be detected in this population in a behavioural study, specifically here in view of the complexity of the between-groups design utilised in chapter 3. Based on this albeit tentative evidence from chapter 3, this chapter will further explore these potentially subtle glucose effects using EEG to collect data for the neural correlates of episodic memory and will investigate the notion that effects may be too subtle to detect in behavioural data. This chapter incorporated measures of glucoregulatory control and event related potentials alongside behavioural measures to investigate the impact of both glucoregulation

and glucose ingestion on recognition memory in a population of healthy non-diabetic young adults. Specifically, this chapter investigates the role of glucoregulation on the episodic memory of emotional words. Furthermore, to elucidate this further, EEG was employed to assess whether any early effects of glucoregulation, which may not be detected in behavioural data, can be seen in the neural correlates of memory processes. This chapter seeks neurophysiological evidence of glucoregulatory control and/or glucose ingestion modulating recognition memory in a population of healthy non-diabetic young adults and as such provide early indications of the potential cognitive decrements associated with T2DM.

This chapter sought to augment current knowledge by identifying clear evidence of the early onset of cognitive decrements potentially associated with poor glucoregulatory control. Two predictions were made based on the two contending theories. The task domain related research question proposed that, if enhancement was subserved by the hippocampus, glucose would preferentially target recollection, rather than familiarity, as such modulating LPC amplitudes in the posterior region across the later 400-800ms time window. If task demand is the more important determinant, then it was predicted that a more global glucose facilitation would enhance both recollection and familiarity, modulating amplitudes for recollection in the 400-800ms time window, but additionally modulating FN400 amplitudes for familiarity judgements in the earlier 300-500ms time window (Curran, 2000; Woodruff et al., 2006b). Based on the above research suggesting that glucose preferentially targets individuals with challenged glucoregulatory control, it may also be predicted that enhancement effects are more likely to be seen in 'poorer' regulators. The principal aim of this chapter is to investigate the effect of glucoregulatory control and circulatory blood glucose levels on the physiological responses (heart rate) and the neural correlates of episodic memory for emotional words and the following research questions were posited:

- Will ingested glucose or glucoregulatory control mediate the ERP correlates of the encoding and recognition processes of memory. Specifically, this will address whether differences in neural activity between by 'better' and 'poorer' glucoregulators are evident.
- Will ingested glucose or glucoregulatory control mediate recognition accuracy. Evidence for this will provide support for the notion that glucose preferentially targets 'poorer' regulators.
- Does raising circulating blood glucose levels preferentially target the hippocampal domain, with the enhancement of recollection, but not familiarity as would be observed in the

behavioural data? Or is any facilitation more global with high cognitive demand enhancing both recollection and familiarity.

- Does ingested glucose mediate the memory strength, as such explicit recollection or familiarity for correctly recognised words, and in turn ERP correlates of recognition memory? This would suggest a more global facilitation which would modulate ERP amplitudes for both recollection and familiarity. Should the effect be domain specific and subserved by the hippocampus then only ERP amplitude modulation of recollection would be observed.
- Do interactions between glucoregulatory control and ingested glucose target 'poorer regulators' rather than 'better' regulators in this population. Evidence of this would support the potential for early identification of glucoregulation related cognitive changes in this pre-clinical compromised population.
- Does glucose ingestion and/or glucoregulatory control modulate the physiological response to the exposure to neutral and emotionally valenced words. If heart rate measures of beats per minute are modulated by ingested glucose it would be expected that BPM would accelerate in response to emotional stimuli following glucose.
- Do glucoregulatory control and/or ingested glucose impact on attentional resources during the Flanker conflict task. If glucoregulatory control impacts on sustained attention, poorer regulators would have diminished performance, compared to better regulators, in the placebo condition. If glucose enhancements are only seen for populations with challenged glucoregulatory control, then glucose ingestion would benefit poorer glucoregulators.

4.2 Materials and Method

4.2.1 Design

A randomised placebo controlled, double-blind two visit crossover design. Analyses of both behavioural and neurophysiological data were conducted separately on encoding data, recognition accuracy data and subjective recognition data (Remember/Know paradigm). Apart from glucoregulation, which was a between- subjects variable, all other variables were within-subjects. The OGTT data was analysed via a one-way ANOVA and all other analyses were mixed factorial ANOVA.

4.2.2 Participants

Twenty-one, self-reportedly healthy young adults (9 males, mean age 21.57 years, SD 4.46) took part in this study (see Appendix 4.1 and Appendix 4.2 for a complete list of demographic and health screen data) which was approved by the Staffordshire University Psychology Ethics Committee. Participants were psychology students who were recruited from the undergraduate cohort. Prior to taking part in the study informed consent was obtained from all individual participants included in the study. Health and demographic screening, including the faculty blood-screening questionnaire were completed to ascertain whether prospective participants met the exclusion/inclusion criteria of the study. Participants were screened for any food allergies which related to the treatments employed in the study and any glucoregulatory/metabolic disorders, such as diabetes; individuals with heart rate disorders (Arrhythmias), or phenylketonuria were excluded; smokers were also excluded. All participants were asked to self-report whether they were in good health, free from prescription drugs (excluding contraceptives) over-the-counter medicines, illicit and recreational drugs (including nicotine). Demographic and morphometric information was collected (BMI mean 25.32, *SD 4.28;* WHR 0.84, *SD 0.05*). Participants attended three sessions; session one was to assess participants' glucoregulation and training was given for the cognitive tasks that were to be conducted during the two test visits. Before each visit participants fasted overnight for 12 hours during which time, they could only drink water. On completing the study, students received twenty-five 'Research Participation Vouchers'.

4.2.3 Blood Glucose Levels

At the first visit, participants' glucoregulation was assessed via a 75 g dose oral glucose tolerance test (OGTT) following a 12 hour overnight fast (water permitted). Finger prick blood samples were taken using a Roche Accutrend Plus diagnostic instrument and Accutrend Glucose Strips. Circulatory blood glucose levels were measured at baseline and then at 30, 60, 90 and 120-minutes post glucose load. The OGTT assessed circulatory blood glucose at 5 time points and there are various ways in which these measures can be utilised to calculate an individual's glucose tolerance levels. The method used in this study is defined by individual's recovery of evoked levels, calculated by subtracting fasting baseline blood glucose level from the 60-minute OGTT glucose level (Craft et al., 1994; Donohoe & Benton, 2000; Kaplan et al., 2000). Relative to the four post-glucose dose measures of the OGTT , Messier et al (2003) argues that, in terms of the glucose enhancement of memory, the 60-minute time point is correlated with memory tasks. In terms of this study, this glucoregulation index

encompasses the time frame of mood and satiety measures and cognitive assessments conducted on study day visits. To facilitate a median split, which assigned participants into 'poorer' and 'better' glucoregulation types, evoked levels of blood glucose were calculated by subtracting baseline fasting blood glucose levels the 60-minutes post dose blood glucose level for each participant. On study days blood glucose levels were measured at baseline, pre-test (10 minutes post-dose) and post-assessments (approximately 45 minutes post-dose).

4.2.4 Treatments

Prior to the study a treatment orders were randomised and assigned to participant numbers. Treatments comprised of a 200ml drink with 20 ml of Robinsons Sugar Free Orange Cordial to which had been added either 25g of glucose (from myprotein.co.uk) or 5 saccharin 'Mini-Sweeteners' (Hermesetas brand). This is a standard drink, matched for sweetness and oral texture (Scholey, et al., 2001) used by similar studies in the literature. This is also the treatment combination which was deemed most appropriate based on the outcomes of chapters 2 and 3. After drinks had been made, they were labelled by a disinterested third party who was not involved in the study; this ensured the 'double-blind' status of the study. All drinks were prepared on the day prior to testing and were stored in sealed containers overnight in a refrigerator prior to serving. Whilst the participants were blind to their allocated treatment, they were fully informed as to the ingredients used in treatments to be consumed throughout the study.

4.2.5 Heart Rate

Heart rate was monitored throughout using the Biopac MP36 Data Acquisition Unit. Electrodes were Vinyl Electrode Stress-Gel electrodes, EL503 for ECG, attached to participants' ankles and right wrist. During the encoding phases mean heart rate was measured over one, two and three seconds after presentation of each word, as such a measure of any effects of valence at the initial viewing of words.

4.2.5.1 Heart Rate Methodology

Heart rate was monitored throughout using electroencephalogram (ECG) data collected by a Biopac MP36 Data Acquisition Unit. Electrodes were Vinyl Electrode Stress-Gel electrodes, EL503 for ECG, attached to participants' ankles and right wrist. During the encoding phase mean heart rate was measured over one, two and three seconds after presentation of each word, as such, a measure of

any effects of valence at the initial viewing of words. In chapter 4 glucoregulation effects of baseline resting heart rate were explored by recording heart rate during the 60 second calibration period prior to the commencement of the tasks. Prior to analysis all data was cleaned using the Biopac (Linton Instrumentation) guidance.

4.2.6 Neurophysiological Measures

4.2.6.1 EEG Methodology

The EEG methodology utilised in this thesis involved the recording of event-related potentials (ERPs) while participants performed recognition memory tasks. Additionally, whereas no data can be collected from behavioural studies during the encoding phase of recognition memory, by utilising EEG it is possible to collect neurophysiological data when employing ERP methodologies.

Neurophysiological data were recorded in reference to the vertex electrode (Cz) at a rate of 1 kHz from 67 electrode sites situated in compliance with the 10-20 convention (Klem et al., 1958) using an Easycap system (Easycap™, Brain Products, Germany) and a Neuroscan SynAmps RT amplifier. Vertical and horizontal electrooculograms (EOG) were recorded at electrodes placed at the outer canthus of each eye (HEOG) and above and below the left eye (VEOG), see below for a diagraph of all electrodes. Impedances were kept below 10 kΩ for all electrodes and with EEG activity filtered on-line with a band pass between 0.1 Hz and 200 Hz and re-filtered off-line with a 30 Hz low pass filter. Post hoc removal of eyeblinks was conducted offline using CURRY 7 (Neuroscan Inc., El Paso, Texas, USA) software using the principal component analysis (PCA) method set to the Global option. Epochs were created for each task, ranging from 100 to 1000 ms post stimulus onset. Individual averages were re-referenced to a common average reference and baseline correction was performed in reference to electrical activity 200 ms pre-stimulus. Electrodes chosen for analysis was based on *a priori* assumptions derived from previous glucose related word recognition research, see Figure 4.1 and Table 4.1 below.

The electrode arrays which are commonly analysed in the episodic memory literature comprise of 3 anterior electrodes (F3, Fz, F4) and 3 posterior electrodes (P3, Pz, P4). Typically, in recognition memory experiments, the anterior array is considered to reflect familiarity processes and the posterior array is considered to reflect recollection processes (Addante et al., 2012; for a review see Rugg & Curran, 2007; Yonelinas et al., 2005). For example, ERP data for the FN400 component is

typically at the anterior electrodes and the for the LPC component from the posterior electrode. As the work conducted in this thesis is of an exploratory nature, specifically investigating differences in glucose and glucoregulatory control, all 6 electrodes will be included in the analysis. Anterior and posterior regions were included in each analysis to ascertain whether there were differences between the anterior and posterior electrode sites. Anterior and posterior electrode selections provided two levels of a region variable; right, left and midline electrode sites comprised the three levels of a hemisphere variable.

Figure 4.1 Electrode plan, showing sites used for analysis. Reference and ground locations and vertical and horizontal electrooculogram (VEOG and HEOG) eye positions.

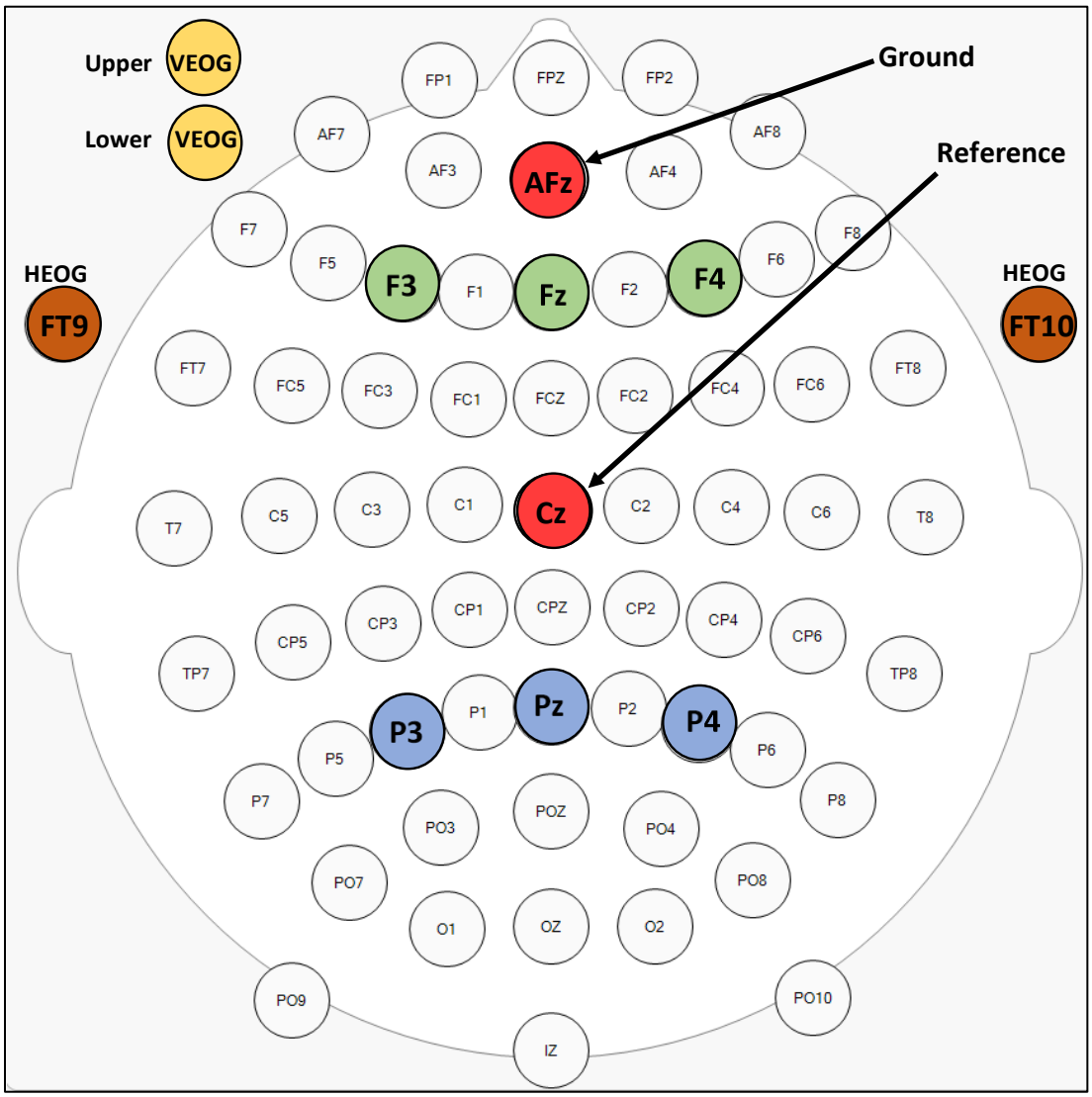


Table 4.1 Arrangement of the horizontal and vertical electrodes used in all ERP analyses.

		Vertical		
		Left	Midline	Right
Horizontal	Anterior	F3	Fz	F4
	Posterior	P3	Pz	P4

4.2.6.1.1 Global Field Power

Global field power analysis classifies the average strength of electrical activity over the scalp (Yamada et al., 2004). To further refine the latency windows of these *a priori* components global field power analysis will be conducted on the data for each of the EEG related analyses. To accomplish this an average across all participants and all conditions will be calculated and a global field power (GFP) analysis will be applied to identify peaks and latencies. Peak latencies of components will be further checked by separately conducting and comparing the GFPs for both treatment groups. These checks will ascertain whether the chosen latency windows for each of the components is appropriate for the respective analyses.

4.2.6.1.2 A Note on 'Difference Waveforms'

A common design in neurophysiological experiments is to utilise a method which 'subtracts' one condition from another. This is frequently found in ERP studies of recognition memory, for example a subtraction between the amplitudes arising from 'old' recognitions and 'new' recognitions which would result in one 'difference waveform'. In the episodic memory literature this is referred to as an 'old-new difference effect'. However, Picton et al. (2000) advises that this is an unreliable practice because other changes of physiological factors, such as differences in the latencies of amplitude peaks are not taken into account. ERP analyses throughout chapters 4 and 5 have been conducted on separate waveforms for each condition e.g., 'old' and 'new' recognitions.

4.2.7 Assessments

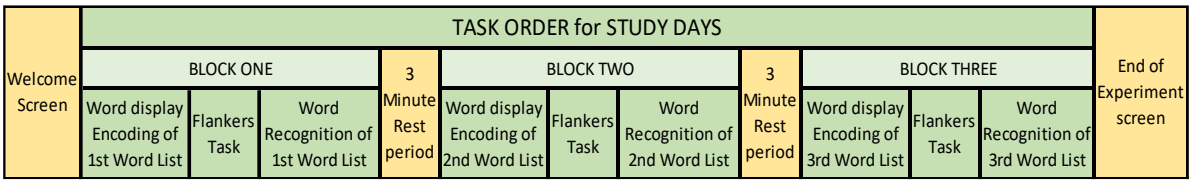
4.2.7.1 Assessment of Mood and Physical and Mental States

To ascertain subjective measures of mood , Bond Lader Mood Scales and Physical and Mental State Scales were completed. The procedure was identical that completed in Chapter 3, see section 3.2.5 for details.

4.2.7.2 Cognitive Assessments

On study days cognitive task assessments were presented in three 'blocks', each with identical formats. The study design for this chapter was identical to the design of chapter 3 so that the results would be directly comparable. Across the 2 study sessions six different word lists were used and no words were interchangeable between blocks and visits, see Figure 4.2 below for a schematic of the study day task order. Participants were instructed to sit quietly and relax for three minutes between blocks.

Figure 4.2 Schema of task order on study days



4.2.7.3 Word Display Encoding

The encoding phase for the current Chapter is identical to that used in Chapter 3, see section 3.2.6.1 for full details.

4.2.7.4 Flanker Inhibition Task

Participants were presented with a conflict task which also serve as a word retention filler task between word encoding and recognition phases. The task presented in the current study was identical to that performed in Chapter 3, see section 3.2.4.3 for full details.

4.2.7.5 Word recognition

The word recognition phase of the assessments was identical to the one conducted in Chapter 3, see section 3.2.6.2 for details.

4.2.8 Procedure

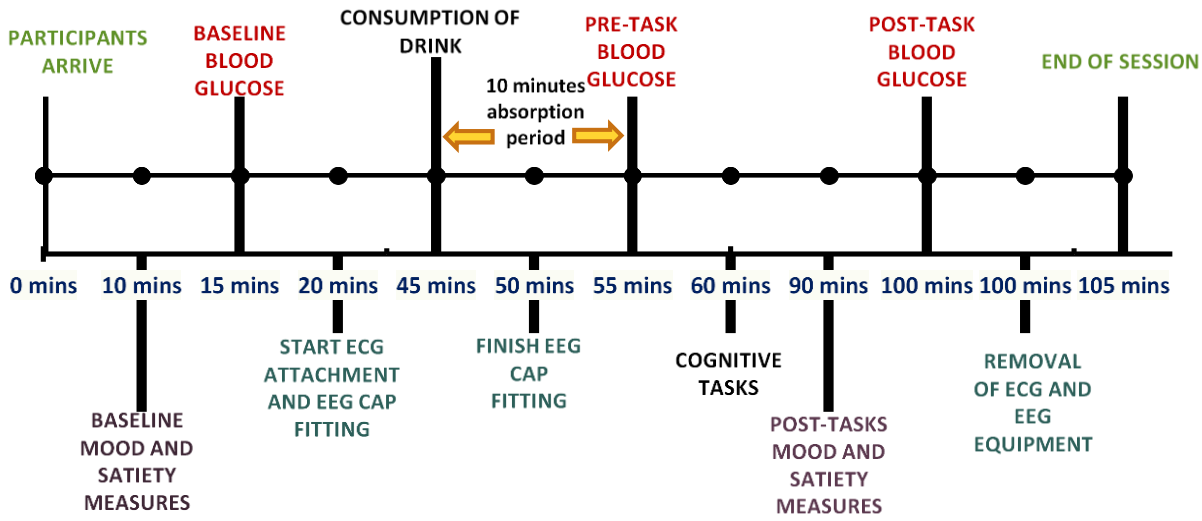
The purpose of the first session was to conduct an Oral Glucose Tolerance Test (OGTT), (see section 1.2.3) and give participants verbal and on-screen task training, they were given a choice of starting time and attended the laboratory between 8.00 am and 9.30 am after a 12 hour fast. Subsequent study day visits were time matched to their starting time for the initial visit to ensure uniformity. Subsequent visits were scheduled with a minimum washout period of 48 hours. Before the first session began health screening and informed consent was sought. The researcher ensured participants were clear on what was expected of them, checked the screening forms to ensure that they met the inclusion criteria and invited questions. Participants' height, weight, waist, and hip measures were taken by the researcher and recorded on the health screen form, for all demographic details see Appendix 4.1 and Appendix 4.2.

The OGTT data was used to assess individuals' glucoregulation and the outcomes of this enabled a median split which allocated participants to either 'better' or 'poorer' glucoregulator groups. A practice battery of tests with verbal instruction as well as task related onscreen instructions was performed to train participants on each of the tasks that were used during the study day visits. The practice battery comprised of 12 repetitions of each of the cognitive tasks lasted for approximately 15 minutes and was performed during one of the 30-minute waiting times between OGTT blood sampling. No data was collected from these practice sessions. Participants were given an overview of the procedure for the study days, shown the laboratory and the equipment to be used and given details about hair washing/showering facilities.

On study day visits participants were seated in front of a computer in the EEG laboratory. The experimental or placebo drink was consumed 10 minutes prior to task commencement; this is considered to be sufficient time for the 25g glucose dose to be absorbed and ensure that during the glucose visit participants blood glucose is elevated throughout the duration of the cognitive tasks. As this was a within-groups comparisons were made across conditions rather than do a baseline assessment at each visit. The rationale for this was that as the sessions already lasted for a minimum

of 1.5 hours, taking into account the capping process, blood sampling and drink consumption and absorption, adding a further 45 minutes of sitting still because of EEG and ECG electrodes would have been tiring and uncomfortable for participants. Additionally, and importantly the electrical impedances of the EEG electrodes, which were all kept to a minimum, tend to drift with time and movement, and as this would all be reflected in the post-treatment data, comparison between baseline and post-treatment would not have been robust. Comfort and wellbeing of participants was also a consideration. The researcher was in an adjoining control room and there was two-way microphone/speaker communication with the participant throughout the session. A non-recording web camera was also directed at the participants' computer screen so that the researcher could monitor progression. The timeline of study visits can be seen in Figure 4.3. After the equipment had been removed participants were offered hair washing facilities.

Figure 4.3 Schematic of study day running order with cognitive assessment highlighted in boxes.



4.3 Statistical Analyses

All analyses were conducted using mixed factorial ANOVAs and any significant main effects or interactions were explored using post hoc pairwise comparisons with Bonferroni corrections.

4.3.1 Data Cleaning

Data was screened and cleaned prior to analysis. Where non-sensible values, missing data or outliers were found these were omitted from the analyses using listwise deletion. Datasets were checked for assumptions of mixed-groups ANOVA, as such, independence of scores, normal distribution, and homogeneity of variance sphericity where the within-groups variables had 3 or more levels.

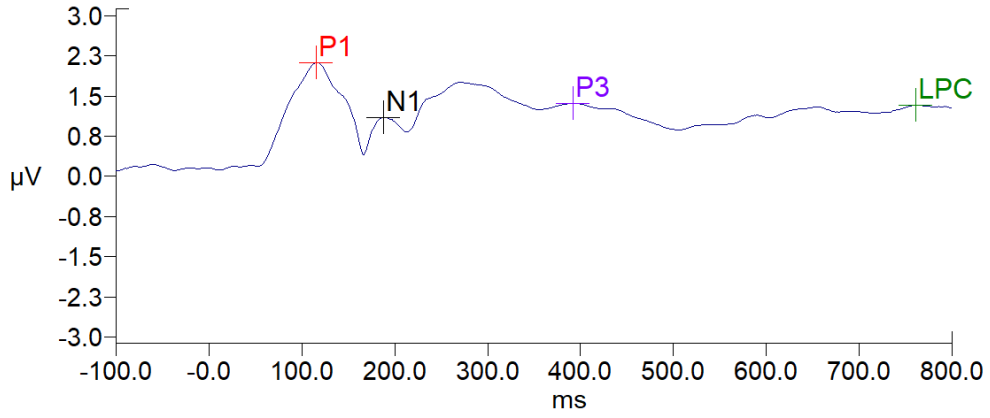
4.3.2 ERP Amplitude Analysis

As EEG data is rarely homogenous, to compensate for these violations in the analysis of repeated measures ANOVA designs, Greenhouse-Geisser corrections were applied to all ERP analyses (Picton et al., 1995; Picton et al., 2000) to ensure that type 1 error rates were not inflated by the potential lack of homogeneity found in EEG data (Greenhouse & Geisser, 1959).

4.3.2.1 Word Recognition Encoding data

Encoding analyses were conducted for four ERP components which are suggested to be associated with sensitivity to the emotional, attentional and recognition aspects of visual word processing: specifically, the P1, the N1, the P3 and the LPC components (see section 1.6.1.1 for a description of these components). Determination of the relevant time windows was based on *a priori* research and these time windows were then refined via the calculation of global field power (see Figure 4.4 below). Observation of the P1 component was from 50 to 170ms post stimulus presentation, the N1 negative going component over the 165 to 220ms time window; the P3 positive going component over the 300 to 500ms time window and the LPC positive going component over the 400 to 800ms time window.

Figure 4.4 Global field power classification of the encoding phase ERP components

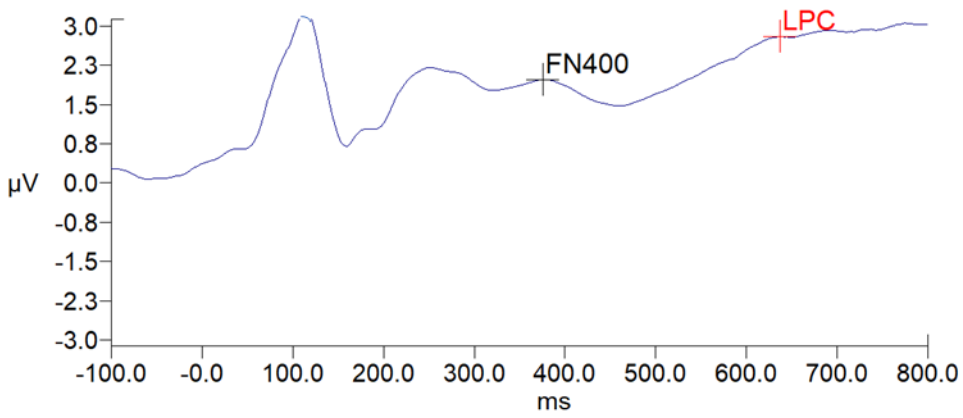


Word recognition encoding analysis was via mixed factorial ANOVAs, conducted on data from 3 anterior and 3 posterior electrodes (F3, Fz, F4 and P3, Pz and P4). Anterior and posterior electrode selections provided two levels of a region variable; right, left and midline comprised the three levels of a hemisphere variable. Thus, a five-way mixed factorial ANOVA (Treatment(2) x Region(2) x Valence(3) x Hemisphere(3) x Glucoregulation(2)) was conducted.

4.3.2.2 Word Recognition Old/New Accuracy

Conventionally the FN400 component old-new effect is investigated in the 300 – 500ms time window and is believed to reference familiarity and at mid-anterior sites, and in the 400 – 800ms time window, the LPC, is thought to reference recollection. The chosen time windows were based on *a priori* research and then refined by the calculation of global field power (see Figure 4.5 below). Subject to these refinements the FN400 analyses were conducted in the 300 to 500ms time window and the LPC analyses over the 400 to 800ms time window.

Figure 4.5 Global field power classification of the recognition phase ERP components



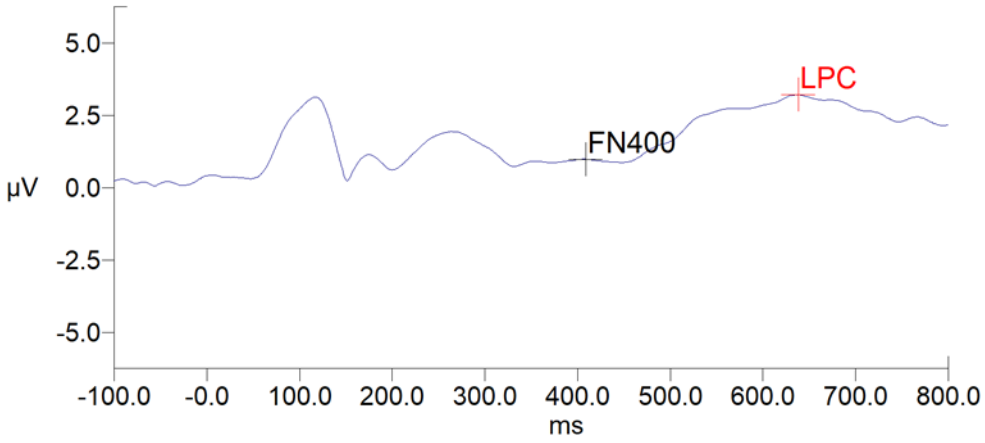
Word recognition old/new accuracy analysis was via mixed factorial ANOVAs conducted on data from 3 anterior and 3 posterior electrodes (F3, Fz,F4 and P3, Pz and P4). As the work of this thesis is an exploratory investigation of glucoregulation differences, both anterior and posterior regions were included in each analysis to ascertain whether there were differences there were differences between the two regions. As before, anterior, and posterior electrode selections provided two levels

of a region variable; right, left and midline comprised the three levels of a hemisphere variable. Thus, a five-way mixed factorial ANOVA (Treatment (2) x Region (2) x Valence (3) x Hemisphere (3) x Glucoregulation (2)) was conducted for both the FN400 component and the LP component.

4.3.2.3 Word Recognition Remember/Know

ERP data, relative to participants' subjective experience of remembering or knowing correctly recognised old words, was collected. Analysis investigating the FN400 component was conducted in the 300 to 500ms time window and the LP component was explored in the 400 to 800ms time window. The chosen time windows were based on a priori research and then refined by the calculation of global field power (see Figure 4.6 below). Subject to these refinements the FN400 analyses were conducted in the 300 to 500ms time window and the LPC analyses over the 400 to 800ms time window.

Figure 4.6 Global field power classification of the subjective recognitions Remember/Know ERP components.



Word recognition remember/know analyses were via mixed factorial ANOVAs, conducted on data from 3 anterior and 3 posterior electrodes (F3, Fz,F4 and P3, Pz and P4). Anterior and posterior regions were included in each analysis to ascertain whether there were differences between the anterior and posterior electrodes. As before, anterior, and posterior electrode selections provided two levels of a region variable; right, left and midline comprised the three levels of a hemisphere

variable. Data was subjected to mixed factorial six-way (Treatment (2) x Region (2) x Recognition Type (2) x Valence (3) x Hemisphere(3) x Glucoregulation (2) ANOVAs.

4.4 Summaries

Summaries of measures are included following the results for each of the mood and physical state assessments and the cognitive tasks results.

4.5 Physiological Results

4.5.1 Blood Glucose Levels and Glucoregulation

See Table 4.2 for participant demographics and OGTT blood glucose levels.

Table 4.2 Demographic and oral glucose tolerance test blood glucose data of better and poorer regulators.

Measure	Better regulators				Poorer Regulators			
	Males		Females		Males		Females	
	Mean	*(SEM)*	Mean	*(SEM)*	Mean	*(SEM)*	Mean	*(SEM)*
Age (years)*	19.20	(0.20)	25.50	(3.50)	25.50	-3.5	21.80	-3.07
Education (years)*	14.00	-0.77	15.00	-0.01	15.00	(0.00)	14.60	-0.4
BMI (kg/m^2)#	23.81	-1.62	27.62	-0.15	27.62	-0.15	24.06	-1.44
Waist/Hip Ratio (W/H)#	0.88	-0.01	0.88	-0.01	0.88	-0.01	0.81	-0.01
Fasting Glucose (mmmol/l)	4.31	-0.13	4.33	-0.23	4.84	-0.05	4.17	-0.16
30 Minute Glucose (mmmol/l)	7.14	-0.39	6.52	-0.62	7.7	-0.87	7.9	-0.26
60 Minute Glucose (mmmol/l)	5.26	-0.24	5.49	-0.56	8.48	-0.2	8.19	-0.63
90 Minute Glucose (mmmol/l)	5.16	-0.33	4.91	-0.31	7.11	-0.22	7.17	-0.92
120 Minute Glucose (mmmol/l)	4.45	-0.39	4.88	-0.16	6.59	-0.03	6.39	-0.53
Evoked glucose levels (60 min - fasting)	0.95	-0.29	1.16	-0.4	3.64	-0.25	4.02	-0.6

Note: * = participant' self-report measures; # = measures taken by researcher

4.5.1.1 Oral Glucose Tolerance Test

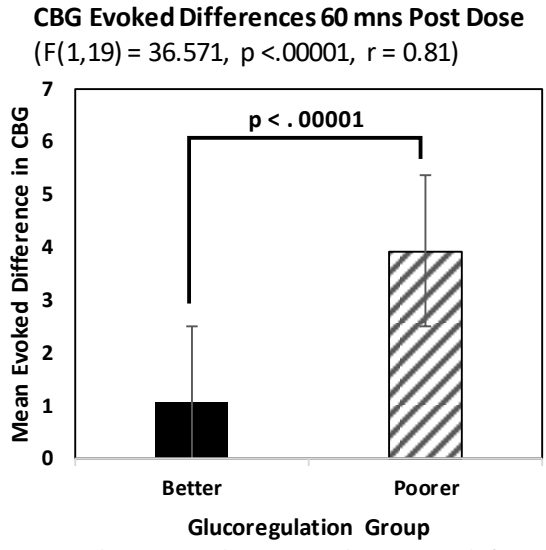
See Table 4.3 below for better and poorer glucoregulators OGTT means and SEMs

Table 4.3 Oral Glucose Tolerance Test. Means, SEMs and significant effects are indicated (Gluc = Glucoregulation Group) *(*p<0.001, **p<.005*)**

Outcome	Timepoint	Glucoregulation Group	N=	Mean and SEM			Significant Effects
				Means	±	SEM	
OGTT Blood Glucose Levels	Baseline	Better	11	4.32	±	0.44	-
		Poorer	10	4.36	±	0.63	
	30 minutes	Better	11	6.80	±	1.24	-
		Poorer	10	7.71	±	1.07	
	60 minutes	Better	11	5.38	±	1.03	Gluc ***
		Poorer	10	8.29	±	1.07	
	90 minutes	Better	11	5.02	±	0.73	Gluc ***
		Poorer	10	7.22	±	1.55	
	120 minutes	Better	11	4.68	±	0.66	Gluc **
		Poorer	10	6.09	±	1.06	

Analysis of blood glucose levels over the two-hour OGTT, as would be expected, indicated a normal response curve of overall mean blood glucose levels for a cohort of healthy young adults (see Figure 4.8 a). A one-way ANOVA revealed a significant difference in evoked blood glucose levels (evoked levels of circulatory blood glucose (CBG) at baseline were subtracted from levels at 60 minutes post dose) for both better and poorer glucoregulators as determined via the median split ($F(1,19) = 36.571$, $p < .001$, $r = 0.81$), see Figure 4.7.

Figure 4.7 OGTT Comparison of glucoregulation groups as assigned via the median split of evoked differences in circulating blood glucose levels at 60 minutes post glucose load (see figure key for significance)



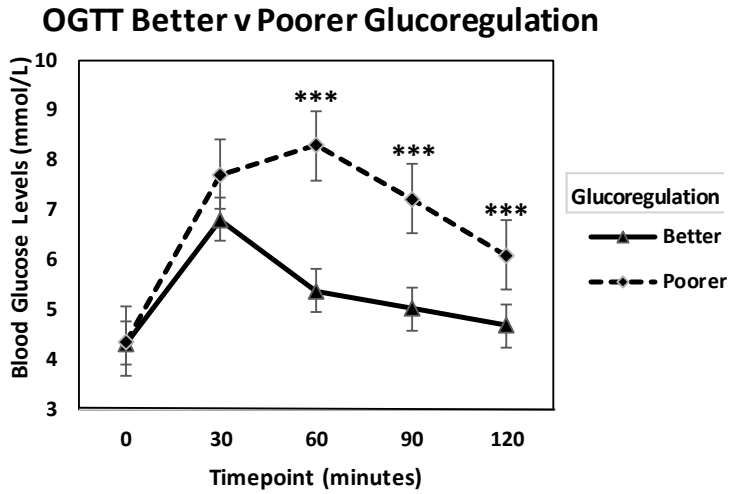
One-way ANOVAs conducted at each time point to assess differences between glucoregulation groups can be seen below in Table 4.4.

Table 4.4 OGTT one-way ANOVAs showing differences at five time points between better and poorer glucoregulator groups. F values, degrees of freedom, significance levels and effect sizes are shown.

Time Point	df	F	p value	r
Baseline	(1,20)	0.020	0.889	0.03
Dose + 30	(1,20)	3.153	0.092	0.38
Dose + 60	(1,20)	40.362	<0.001	0.82
Dose + 90	(1,20)	17.782	<0.001	0.70
Dose + 120	(1,20)	13.521	0.002	0.65

For 'better' vs 'poorer' glucoregulators, as grouped via the median split, a two-way ANOVA indicated a time x glucoregulation interaction ($F(4,76) = 9.300$, $p < .001$, $r = 0.30$). Post hoc analyses showed that following the glucose load and compared to better glucoregulators, poorer glucoregulators had significantly higher levels of blood glucose at 60 minutes ($t(19) = 6.359$, $p < .001$); 90 minutes ($t(19) = 4.213$, $p < .001$) and at 120 minutes post ingestion ($t(19) = 3.673$, $p = .002$). See Figure 4.8b).

Figure 4.8 OGTT blood glucose levels for 'better' vs 'poorer' glucoregulators.(***p<.001)



4.5.1.2 Test Visit Blood Glucose Levels

Prior to the main analysis, One-way ((2) Glucoregulation) ANOVAs conducted on baseline test visit blood glucose levels found that there were no significant differences between the glucoregulation groups for either the glucose test visits ($F(1,19) = 0.007$, $p = .933$, $r = 0.02$) or the placebo visits ($F(1,19) = 1.026$, $p = .325$, $r = 0.23$).

See Table 4.5 below for the means and SEMs of the primary analysis, significant effects and interactions for test visit blood glucose levels can be found in below.

Table 4.5 Test visit blood glucose levels. Means, SEMs and significant effects and interactions are indicated (*Ti = Time, Tr = Treatment, ***p<0.001*)

Outcome	Timepoint	Glucoregulation	N=	Glucose			Placebo			Significant Effects and Interactions
				Means	±	SEM	Means	±	SEM	
Blood Glucose Levels	Baseline	Better	11	4.45	±	0.11	4.48	±	0.16	Ti *** Tr*** Ti x Tr ***
		Poorer	7	4.49	±	0.20	4.75	±	0.14	
	Pre-Tasks	Better	11	5.53	±	0.23	4.39	±	0.18	
		Poorer	7	5.68	±	0.23	4.37	±	0.18	
	Post-Tasks	Better	11	6.23	±	0.17	4.20	±	0.14	
		Poorer	7	6.40	±	0.38	4.30	±	0.20	

The primary three-way glucoregulation x treatment x time interaction was non-significant (F(2,32) = 0.320, p = .729, r = 0.04). Significant main effects and interactions are shown in Table 4.6 below. Only significant higher order interactions are reported in the text.

Table 4.6 Test day blood glucose levels ANOVA. F values, degrees of freedom, significance levels and effect sizes for interactions and main effects are shown.

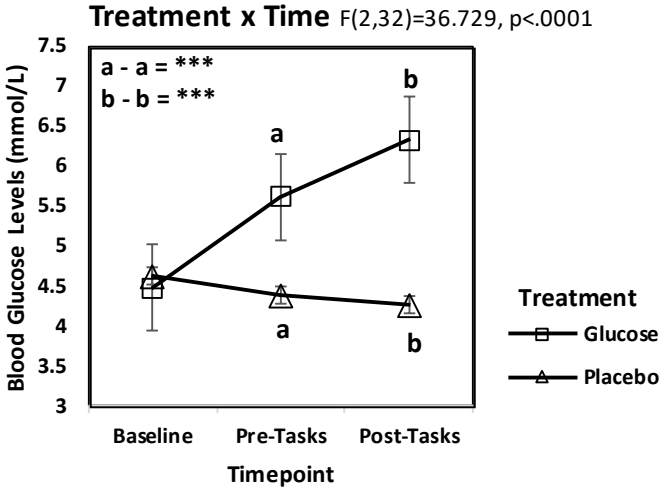
Main Effects/ Interactions	Df	F	p value	r
Treatment x Time	(2,32)	36.729	<0.001	0.24
Treatment	(1,16)	151.417	<0.001	0.27
Time	(2,32)	17.653	<0.001	0.16

As expected, there was a treatment x time interaction (F(2,32) = 36.729, p<.001, r = 0.24) (see Table 4.6 above and Table 4.7 below for interaction means and SEMs). Pairwise comparisons revealed that pre-task blood glucose levels were higher following glucose (Mean 5.61, SEM 0.17) compared to following placebo (Mean 4.38, SEM 0.14), (t(16) = 9.397, p<0.001). Also, at post-tasks blood glucose levels were higher following glucose (Mean 6.32, SEM 0.23) compared to following placebo (Mean 4.25, SEM 0.11), (t(16) = 8.368, p<0.001), see Figure 4.9 below.

Table 4.7 Test day blood glucose means and SEMs depicting the treatment x time interaction.

Treatment	Time	Mean	±	SEM
Glucose	Baseline	4.467	±	0.127
	Pre-Tasks	5.608	±	0.173
	Post-Tasks	6.318	±	0.233
Placebo	Baseline	4.617	±	0.117
	Pre-Tasks	4.378	±	0.138
	Post-Tasks	4.251	±	0.111

Figure 4.9 Test-visit time x treatment interaction. See figure key for significance levels. (**p<.001).* Bars show standard error.**



4.5.1.2.1 Summary of Blood Glucose Results

As expected, the Oral Glucose Tolerance test showed that all participants were within the normal range for fasting blood glucose for healthy young adults. Utilising the median split, which was applied to assign participants to 'better' and 'poorer' glucoregulation groups, significant differences in blood glucose levels between the two groups were seen at 60, 90 and 120 minutes following the glucose dose. Blood glucose levels were higher for the poorer regulators than for the better regulators. Also, as expected test-visit blood glucose levels were higher following glucose compared to placebo, although unexpectedly there was no significant difference between glucoregulation groups.

4.5.1.3 Heart Rate

See Table 4.8 below for the means and SEMs for the ECG analysis of heart rate means over 0 - 1 second, 0 - 2 seconds and 0 - 3 seconds post presentation of stimuli during the encoding phase.

Table 4.8 Mean heart rate levels for better and poorer glucoregulators at 1 second, 2 seconds and 3 seconds post presentation of negative, positive and neutral words. Means and SEMs are shown. There were no significant effects or interactions.

Outcome	Emotion	Time	Glucoregulation	N =	Glucose			Placebo			Significant Effects and Interactions
					Means	±	SEM	Means	±	SEM	
Mean Heart Rate	Negative	1 second	Better	11	71.26	±	2.04	70.55	±	2.21	None
			Poorer	10	75.12	±	2.07	71.89	±	3.49	
		2 seconds	Better	11	71.46	±	2.02	70.66	±	2.11	
			Poorer	10	75.03	±	2.09	71.77	±	3.54	
		3 seconds	Better	11	71.43	±	1.98	70.44	±	2.14	
			Poorer	10	75.02	±	2.12	71.8	±	3.56	
	Positive	1 second	Better	11	71.68	±	2.00	71.01	±	2.22	
			Poorer	10	75.01	±	2.39	71.36	±	3.4	
		2 seconds	Better	11	71.68	±	1.95	71.07	±	2.24	
			Poorer	10	74.92	±	2.30	71.51	±	3.37	
		3 seconds	Better	11	71.62	±	1.92	71.06	±	2.21	
			Poorer	10	74.91	±	2.19	71.82	±	3.37	
	Neutral	1 second	Better	11	71.50	±	2.01	70.64	±	2.42	
			Poorer	10	74.61	±	2.17	71.38	±	3.32	
		2 seconds	Better	11	71.50	±	2.02	70.39	±	2.41	
			Poorer	10	74.43	±	2.17	71.32	±	3.34	
		3 seconds	Better	11	71.30	±	1.94	70.31	±	2.39	
			Poorer	10	74.73	±	2.18	71.57	±	3.34	

The primary four-way treatment x valence x time x glucoregulation ANOVA was non-significant ($F(4,76) = 0.417$, $p = .796$, $r = < 0.00001$) and did not reveal any significant effects. Similarly, the three-way treatment x valence x glucoregulation interaction was also non-significant ($F(2.38) = 0.310$, $p = .584$, $r = 0.00004$), again with no significant main effects or interactions.

4.5.1.3.1 Summary of Heart Rate Results

There were no significant effects or interactions for measures of heart rate beats per minute assessed during the encoding phase word display.

4.6 Behavioural Results

4.6.1 Assessment of Mood and Physical and Mental States

4.6.1.1 Bond Lader Mood Scales

Prior to the main analysis, one-way ((2) Glucoregulation) ANOVAs conducted on baseline scores found that, with the exception of placebo visits calmness, there were no significant differences in baseline scores between the glucoregulation groups for either the glucose test visits or the placebo

visits for Bond Lader mood measures. Poorer glucoregulators were more calm than better regulators at baseline on placebo visits (F1,19) = 11.823, p = .003, r = 0.62).

See Table 4.9 below for means and SEMs of primary three-way ANOVA.

Table 4.9 Bond Lader Mood Scales. Means, SEMs for better and poorer glucoregulators. Significant effects and interactions are indicated. (Gluc = Glucoregulation, Ti = Time. (*p<0.05), **p<0.005)

Outcome	Timepoint	Glucoregulation	N=	Glucose			Placebo			Significant Effects and Interactions
				Means	±	SEM	Means	±	SEM	
Alert	Baseline	Better	11	51.08	±	4.82	55.04	±	5.02	
		Poorer	10	58.91	±	3.37	56.87	±	3.86	
	Post-Tasks	Better	11	56.03	±	5.03	52.57	±	5.84	
		Poorer	10	62.64	±	4.13	61.71	±	4.34	
Content	Baseline	Better	11	56.80	±	6.25	59.58	±	4.60	
		Poorer	10	64.26	±	3.27	66.04	±	2.13	
	Post-Tasks	Better	11	56.73	±	6.35	59.45	±	4.75	
		Poorer	10	64.98	±	3.95	65.92	±	3.64	
Calm	Baseline	Better	11	52.64	±	3.73	52.64	±	3.31	
		Poorer	10	62.65	±	3.32	68.55	±	3.21	Gluc **
	Post-Tasks	Better	11	52.68	±	3.92	47.82	±	2.11	Ti = *
		Poorer	10	57.75	±	2.96	61.55	±	2.94	

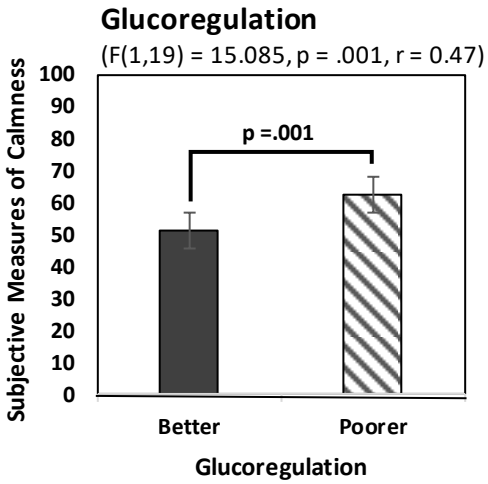
Three-way mixed factorial (Glucoregulation (2) x Treatment (2) x Time (2)) ANOVAs were conducted on each of the subjective measures of 'alertness', 'contentedness', 'calmness'. None of the primary three-way interactions were found to be significant, see Table 4.10 below for statistical justifications.

Table 4.10 Bond Lader Mood Scales. Significant main effects and interactions from the three-way mixed factorial glucoregulation x treatment x time ANOVA. F values, degrees of freedom, significance levels and effect sizes are shown.

Bond Lader Mood Scales	df	F	p value	r
Alertness	(1,18)	0.831	0.374	0.06
Calmness	(1,19)	0.201	0.659	0.03
Contentedness	(1,19)	0.027	0.872	0.01

For measures of calmness there was a significant main effects of glucoregulation (F(1,19) = 15.085, p = .001, r = 0.47) with poorer glucoregulators more calm than better glucoregulators (see **Table 4.9** above for means and SEMs and Figure 4.10 below).

Figure 4.10 Calmness. Main effect of glucoregulation. See figure key for significance levels. Bars show standard error.



4.6.1.2 Physical and Mental State Measures

Prior to the main analysis, One-way ((2) Glucoregulation) ANOVAs conducted on baseline scores found that there were no significant differences in baseline scores between the glucoregulation groups for either the glucose test visits or the placebo visits, for any of the physical and mental state measures.

See Table 4.11 below for means and SEMs of primary three-way ANOVA.

Table 4.11 Physical and Mental State Measures. Means, SEMs for better and poorer glucoregulators.

Outcome	Timepoint	Glucoregulation	N=	Glucose			Placebo			Significant Effects and Interactions
				Means	±	SEM	Means	±	SEM	
Mental Energy	Baseline	Better	11	52.00	±	5.69	48.55	±	3.37	-
		Poorer	10	54.60	±	3.94	56.30	±	3.50	
	Post-Tasks	Better	11	56.45	±	4.19	57.27	±	5.32	
		Poorer	10	53.00	±	4.42	56.50	±	4.93	
Concentration	Baseline	Better	11	58.27	±	2.81	64.00	±	4.05	-
		Poorer	10	58.30	±	4.69	56.80	±	5.45	
	Post-Tasks	Better	11	61.36	±	6.15	54.91	±	6.12	
		Poorer	10	54.40	±	7.04	54.10	±	7.13	
Fullness	Baseline	Better	11	34.36	±	5.81	31.82	±	5.65	-
		Poorer	10	29.70	±	5.59	26.70	±	3.02	
	Post-Tasks	Better	11	36.55	±	5.04	36.73	±	3.88	
		Poorer	10	41.90	±	5.52	31.60	±	6.68	
Physical Stamina	Baseline	Better	11	45.91	±	6.18	47.73	±	4.53	-
		Poorer	10	53.70	±	6.14	49.10	±	6.67	
	Post-Tasks	Better	11	49.09	±	6.45	53.09	±	5.91	
		Poorer	10	47.10	±	6.42	50.80	±	5.63	
Mental Fatigue	Baseline	Better	11	46.27	±	6.08	51.55	±	4.39	-
		Poorer	10	44.90	±	7.02	51.20	±	5.41	
	Post-Tasks	Better	11	44.45	±	6.25	49.27	±	6.85	
		Poorer	10	46.80	±	4.65	51.00	±	6.44	
Hunger	Baseline	Better	11	61.09	±	6.74	64.45	±	4.77	-
		Poorer	10	67.00	±	5.43	68.50	±	5.25	
	Post-Tasks	Better	11	68.36	±	5.47	62.09	±	7.46	
		Poorer	10	65.90	±	5.32	72.40	±	4.68	
Mental Stamina	Baseline	Better	11	52.27	±	5.23	52.82	±	3.84	-
		Poorer	10	52.80	±	5.63	47.60	±	4.87	
	Post-Tasks	Better	11	51.82	±	5.97	51.18	±	5.58	
		Poorer	10	48.10	±	3.87	54.20	±	5.04	
Physically Tired	Baseline	Better	11	49.00	±	5.56	49.27	±	5.98	-
		Poorer	10	54.20	±	7.72	64.10	±	3.85	
	Post-Tasks	Better	11	49.55	±	7.00	53.45	±	7.94	
		Poorer	10	50.70	±	5.47	47.50	±	6.22	
Thirst	Baseline	Better	11	49.91	±	7.26	53.18	±	5.77	-
		Poorer	10	58.90	±	7.30	52.67	±	8.15	
	Post-Tasks	Better	11	45.09	±	7.55	55.36	±	5.04	
		Poorer	10	54.30	±	9.04	60.80	±	6.79	
Mentally Tired	Baseline	Better	11	49.82	±	3.88	48.27	±	2.88	-
		Poorer	10	49.80	±	9.18	39.89	±	6.04	
	Post-Tasks	Better	11	51.73	±	5.25	48.18	±	3.77	
		Poorer	10	47.40	±	7.88	53.40	±	4.22	
Perceived Task Difficulty	Baseline	Better	11	24.09	±	5.35	21.91	±	4.99	-
		Poorer	10	23.90	±	5.88	14.11	±	3.09	
	Post-Tasks	Better	11	24.09	±	4.91	23.18	±	3.77	
		Poorer	10	15.70	±	3.68	24.70	±	5.65	

Three-way mixed factorial (Glucoregulation (2) x Treatment (2) x Time (2)) ANOVAs were conducted on each of the subjective measures of 'mental energy', 'concentration', 'fullness', 'physical stamina', 'mental fatigue', 'hunger', 'mental stamina', 'physical tiredness', 'thirst' and 'mental tiredness'. None

of the primary three-way interactions were found to be significant, see Table 4.12 below for statistical justifications.

Table 4.12 Physical and mental state primary ANOVAs. F values, degrees of freedom, significance levels and effect sizes are indicated.

Physical and Mental States	df	F	p value	r
Mental Energy	(1,19)	0.083	0.776	0.02
Concentration	(1,19)	2.244	0.151	0.24
Fullness	(1,19)	1.284	0.271	0.07
Physical Stamina	(1,19)	0.509	0.484	0.06
Mental Fatigue	(1,19)	0.040	0.844	0.02
Hunger	(1,19)	2.360	0.141	0.27
Mental Stamina	(1,19)	3.573	0.074	0.10
Physical Tiredness	(1,19)	1.261	0.275	0.10
Thirst	(1,19)	0.039	0.846	0.02
Mental Tiredness	(1,19)	2.110	0.164	0.38

There were no significant main effects or interactions for any of the physical and mental state measures.

4.6.1.2.1 Summary of Mood and Physical and Mental State Results

Poorer glucoregulators were seen to be more calm than better regulators and calmer at baseline.

4.6.2 Word Recognition Old/New

4.6.2.1 Overall Memory Performance Accuracy

See Table 4.13 below the means and SEM for the behavioural data analysis of the correct recognitions of old and new words.

Table 4.13 Word Recognition Old/New Overall memory performance accuracy: means, SEMs for the outcomes the 3-way mixed factorial treatment x word type x glucoregulation ANOVA . Significant effects and interactions are indicated (Tr =Treatment, WdTyp = word type, Gluc = glucoregulation (***p<0.001)

Outcome	Glucoregulation	Treatment	N	Word Type	Mean	±	SEM	Significant Effects and Interactions
% Correct Recognitions	Better	Glucose	11	Old	73.74	±	5.64	WdTyp ***
			11	New	90.31	±	2.66	
		Placebo	11	Old	73.64	±	5.34	
			11	New	88.79	±	2.13	
	Poorer	Glucose	10	Old	65.22	±	5.91	
			10	New	90.56	±	2.79	
		Placebo	10	Old	69.45	±	5.60	
			10	New	92.00	±	2.23	

The primary three-way mixed factorial glucoregulation x treatment x word type (old/new) interaction was non-significant (F(1, 19) = 0.032, p = .860, r =0.02).

There was a significant main effect of word type (F1,19) = 21.288, p<.001, r = 0.32); accuracy was greater for correct rejections of new words (Mean 90.41, SEM 1.57) compared to correct recognitions of old words (Mean 70.51, SEM 3.705), (t(19) =4.614, p<.001).

4.6.2.2 Overall Memory Performance Response Reaction Speed

See Table 4.14 below the means and SEM for the behavioural data analysis of the response speeds for correct recognitions of old and new words.

4.14 Overall memory performance response reaction speed: means, SEMs for the outcomes the 3-way mixed factorial treatment x word type x glucoregulation ANOVA . Significant effects and interactions are indicated (Tr =Treatment, WdTyp = word type, Gluc = glucoregulation (p<0.01)**

Outcome	Glucoregulation	Treatment	N	Word Type	Mean	±	SEM	Significant Effects and
Correct Recognitions Response Speed	Better	Glucose	11	Old	1176.55	±	101.83	WdTyp **
			11	New	1085.05	±	90.67	
		Placebo	11	Old	1322.67	±	95.14	
			11	New	1178.03	±	97.51	
	Poorer	Glucose	10	Old	1445.08	±	106.80	
			10	New	1251.82	±	95.10	
		Placebo	10	Old	1491.87	±	99.78	
			10	New	1253.14	±	102.26	

The primary three-way mixed factorial glucoregulation x treatment x word type (old/new) interaction was non-significant (F(1, 19) = 0.004, p = .948, r =0.004).

There was a significant main effect of word type (F1,19) = 8.877, p = .008, r = 0.38); response speeds were faster for correct rejections of new words (Mean 1192.01, SEM 63.592) compared to correct recognitions of old words (Mean 1359.04, SEM 63.59).

4.6.2.3 Old/New Accuracy

See Table 4.15 below the means and SEM for the behavioural data for the Word Recognition accuracy analysis. Significant effects and interactions are indicated.

Table 4.15 Word Recognition Old/New Accuracy. Means, SEMs for the four-way mixed factorial treatment x word type x valence x glucoregulation ANOVA. Significant effects and interactions are indicated (Gluc = glucoregulation, Tr = Treatment, WdTyp = Word Type, Val = Valence, (*p<0.05), **p<0.005, ***P<.001).

Glucoregulation	N	Treatment	Word Type	Valence	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	11	Glucose	Old	Negative	74.85	±	6.23	
	11			Neutral	73.34	±	6.26	
	11			Positive	73.03	±	5.42	
	11		New	Negative	87.27	±	3.02	
	11			Neutral	95.76	±	1.55	WdTyp x Val **
	11			Positive	87.88	±	4.28	
	11	Placebo	Old	Negative	74.85	±	5.70	WdTyp ***
	11			Neutral	72.12	±	7.34	
	11			Positive	73.94	±	4.37	Valence *
	11		New	Negative	86.06	±	2.73	
	11			Neutral	93.64	±	1.68	
	11			Positive	86.67	±	3.01	
Poorer Regulators	10	Glucose	Old	Negative	66.67	±	6.54	
	10			Neutral	63.33	±	6.57	
	10			Positive	65.67	±	5.69	
	10		New	Negative	86.00	±	3.17	
	10			Neutral	97.00	±	1.62	
	10			Positive	88.67	±	4.49	
	10	Placebo	Old	Negative	72.33	±	5.98	
	10			Neutral	70.00	±	7.70	
	10			Positive	66.00	±	4.58	
	10		New	Negative	88.33	±	2.86	
	10			Neutral	95.33	±	1.77	
	10			Positive	92.33	±	3.15	

For the analysis of behavioural data showing the percentages of correct recognitions of old words and correct rejections of new words the primary four-way mixed factorial treatment x word type

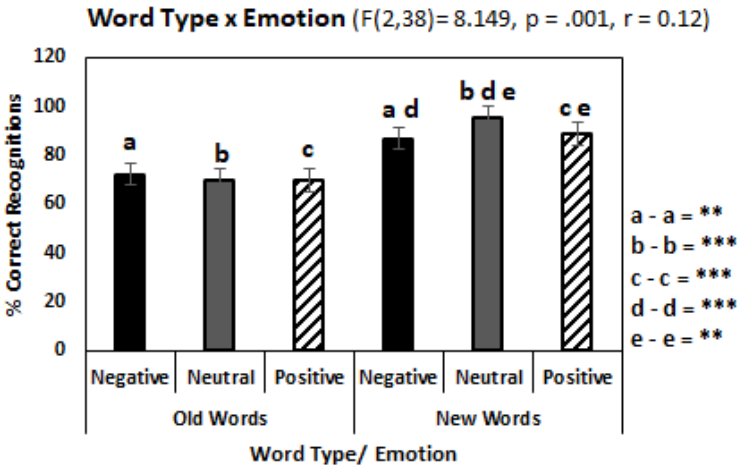
(old/new) x valence x glucoregulation interaction was non-significant (F(2, 38) = 0.897, p = .416, r =0.04). Significant main effects and interactions are shown below in Table 4.16. Only significant higher order interactions are reported in the text.

Table 4.16 Word Recognition Old/New Accuracy. Significant main effects and interactions from the four-way mixed factorial treatment x word type x valence x glucoregulation ANOVA. ANOVA F values, degrees of freedom, significance levels and effect sizes (r) are shown.

Main Effect/ Interaction	df	F	p value	r
Word type x valence	(2, 38)	8.149	.001	0.12
Word Type	(1,19)	21.286	<.001	0.55
Valence	(2,38)	4.374	.020	0.08

The word type x valence interaction (F(2, 38) = 8.149, p = .001, r =0.12) (see Table 4.16 above and Figure 4.11 below), revealed that word type comparisons showed a higher percentage of correct rejections of 'new' negative words than correct recognitions of ‘old’ negative words (t(19) = 3.284, p= .004); a similar pattern was seen for neutral words (t(19) = 5.474, p<.001)) and for positive words (t(19) = 4.184, p<.001). Pairwise comparisons based on valence showed no differences in accuracy for ‘old’ words but for ‘new’ words there were more correct rejections of neutral words compared to negative words (t(19) = 6.753, p<.001) and positive words (t(19)= 3.707, p = .004), see figure keys for pairwise significances.

Figure 4.11 Word Recognition Old/New Accuracy. Word type x valence interaction showing significant 'word type' and 'valence' pairwise comparisons. Figure key shows pairwise comparisons and significance levels.. (*p<.005,***p<.001) Bars show standard error.***



4.6.2.4 Word Recognition Old/New Response Reaction Time

See **Table 4.17** below for the means and SEMs for the behavioural data for the word recognition response reaction time analysis. Significant effects and interactions are indicated.

Table 4.17 Word Recognition Old/New Response Reaction Time. Means, SEMs for the four-way mixed factorial treatment x word type x valence x glucoregulation ANOVA. Significant effects and interactions are indicated (Gluc = glucoregulation, Tr = Treatment, WdTyp = Word Type, Val = Valence,, ; (*p<0.05), **p<0.005, ***P<.001).

Glucoregulation	N	Treatment	Word Type	Valence	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	11	Glucose	Old	Negative	1226.01	±	104.98	
	11			Neutral	1112.83	±	85.75	
	11			Positive	1191.16	±	133.13	
	11		New	Negative	1186.62	±	97.16	
	11			Neutral	986.09	±	88.31	
	11			Positive	1095.45	±	104.65	
	11	Placebo	Old	Negative	1350.84	±	97.18	WdTyp **
	11			Neutral	1271.39	±	120.72	
	11			Positive	1344.24	±	98.96	Valence ***
	11		New	Negative	1227.56	±	107.78	
	11			Neutral	1095.86	±	103.55	
	11			Positive	1218.98	±	101.63	
Poorer Regulators	10	Glucose	Old	Negative	1431.70	±	110.10	
	10			Neutral	1403.26	±	89.93	
	10			Positive	1508.70	±	139.63	
	10		New	Negative	1273.44	±	101.90	
	10			Neutral	1194.43	±	92.62	
	10			Positive	1309.10	±	109.76	
	10	Placebo	Old	Negative	1527.53	±	101.92	
	10			Neutral	1474.67	±	126.62	
	10			Positive	1483.04	±	103.79	
	10		New	Negative	1288.20	±	113.04	
	10			Neutral	1149.37	±	108.61	
	10			Positive	1328.77	±	106.59	

Recognition response reaction times for the word recognition task analysis of correct old/new discriminations were analysed. The primary four-way mixed factorial treatment x word type (old/new) x valence x glucoregulation interaction was non-significant ($F(2, 38) = 0.273$, $p = .763$, $r = 0.02$). Significant main effects and interactions are shown below in Table 4.18.

Table 4.18 Word recognition response reaction time analysis significant main effects and interactions from the four-way mixed measures treatment x word type x valence x glucoregulation ANOVA. F values, degrees of freedom, significance levels and effect sizes (r) are shown.

Main Effect/ Interaction	df	F	p value	r
Word type	(1,19)	8.335	0.009	0.23
Valence	(2,38)	11.574	<.001	0.13

The main effect of word type ($F(1,19) = 8.335$, $p = .009$, $r = 0.23$) showed that response reaction time in milliseconds for correctly rejected new words (Mean 1196.16, SEM 56.39) was faster than for correctly recognised old words (Mean 1360.446, SEM 64.55).

The main effect of valence ($F(2, 38) = 11.574$, $p<.001$, $r =0.13$) revealed faster response speed for neutral words (Mean 1210.99, SEM 53.91) compared to both negative (Mean 1313.99, SEM 53.71), ($t(18)= 4.659$, $p = 0.001$) and positive words (Mean 1309.93, SEM 58.21), ($t(18)= 3.798$, $p = 0.004$).

4.6.2.4.1 Summary of Word Recognition Old/New Behavioural Results

Overall memory performance was not influenced by glucoregulation or treatments, but the main effect of word type showed that correct rejections of new, previously unseen words was more accurate than correct recognitions of old words.

Overall response reaction speed was not influenced by glucoregulation or treatments, but the main effect of word type showed faster responses were made for correct rejections of new, previously unseen words than for correct recognitions of old words.

Analysis of old vs. new accuracy data, the word type x valence interaction showed that for all valence conditions there were more correct rejections of new words compared to correct recognitions of old words. Accuracy was higher for correct rejections of new neutral words compared to both negative and positive words.

Analysis of response reaction time data, the main effect of word type showed faster reaction times for correctly rejected new words compared to correct recognitions of old words. The main effect of valence revealed that reaction times were faster for neutral words relative to both negative and positive words.

4.6.3 Word Recognition Remember/Know

Table 4.19 below shows the means and SEM for the behavioural recognition type analysis of subjective recollection or familiarity judgements (remember or know). Significant effects and interactions are indicated.

Table 4.19 Word Recognition Remember/Know. Means, SEMs for the subjective recognition type analysis via four-way mixed factorial treatment x recognition type x valence x glucoregulation ANOVA. Significant effects and interactions are indicated (Gluc = glucoregulation, Tr = Treatment, RecTyp = Recognition Type, Val = Valence) (*p<0.05), **p<0.005, ***P<.001).

Glucoregulation	N	Treatment	Recognition Type	Valence	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	9	Glucose	Recollection	Negative	31.33	±	3.27	RecTyp x Val *
	9			Neutral	37.13	±	2.32	
	9			Positive	38.26	±	3.06	RecTyp **
	9		Familiarity	Negative	37.10	±	7.70	
	9			Neutral	20.60	±	4.46	Val **
	9			Positive	42.30	±	7.32	
	9	Placebo	Recollection	Negative	42.00	±	4.74	
	9			Neutral	35.82	±	2.29	
	9			Positive	41.43	±	3.74	
	9		Familiarity	Negative	37.91	±	5.42	
	9			Neutral	21.31	±	4.13	
	9			Positive	29.67	±	3.99	
Poorer Regulators	9	Glucose	Recollection	Negative	37.11	±	3.27	
	9			Neutral	34.23	±	2.32	
	9			Positive	33.41	±	3.06	
	9		Familiarity	Negative	40.83	±	7.70	
	9			Neutral	24.39	±	4.46	
	9			Positive	34.78	±	7.32	
	9	Placebo	Recollection	Negative	36.29	±	4.74	
	9			Neutral	35.61	±	2.29	
	9			Positive	33.78	±	3.74	
	9		Familiarity	Negative	38.34	±	5.42	
	9			Neutral	27.00	±	4.13	
	9			Positive	34.66	±	3.99	

For the four-way mixed factorial ANOVA conducted on participants subjective recollection (remember) or familiarity (know) judgements of responses to correctly recognised 'old' previously studied words. The primary treatment x recognition type (R/K) x valence x glucoregulation interaction was non-significant ($F(2, 32) = 0.199$, $p = .821$). Significant main effects and interactions are shown in Table 4.20 below. Only significant higher order interactions are reported in the text.

Table 4.20 Word Recognition Remember/Know. Significant main effects and interactions from the four-way mixed factorial treatment x recognition type x valence x glucoregulation ANOVA.

Main Effect/ Interaction	df	F	p value	r
Recognition Type x Valence	(2,32)	4.057	0.027	0.21
Recognition Type	(1,16)	9.103	0.008	0.14
Valence	(2,32)	6.053	0.006	0.24

There was a significant recognition type x valence interaction ($F(2, 32) = 4.057$, $p = .027$, $r = 0.21$) (see Table 4.20 above and Table 4.21 below for interaction means and SEMs), interaction effects of recognition type pairwise comparisons (see Table 4.22 and Figure 4.12 below) revealed that there were less neutral familiarity judgements made compared to both negative and positive familiarity judgements. Effects of valence on the interaction showed that for neutral words there were more recollection than familiarity judgements.

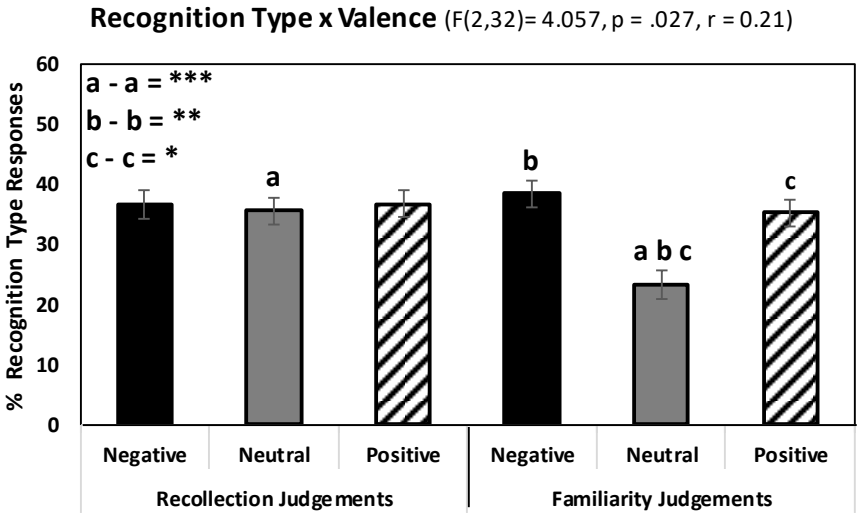
Table 4.21 Word Recognition Remember/Know. Means and SEMs depicting the recognition type x valence interaction.

Recognition Type	Valence	Mean	±	SEM
Recollection	Negative	36.681	±	1.631
	Neutral	35.696	±	1.342
	Positive	36.719	±	1.974
Familiarity	Negative	38.542	±	3.368
	Neutral	23.327	±	2.566
	Positive	35.354	±	2.197

Table 4.22 Word Recognition Remember/Know. Significant pairwise comparisons from the Recognition Type x Region x valence interaction. Pairwise differences, means and SEM, t-values, degrees of freedom and p-values are shown.

Condition / Group	Pairwise Differences	Mean(SEM)	t(22)=	p Value
Familiarity	Negative > Neutral	Negative Words (Mean 38.54, SEM 3.37)	3.543	0.008
		Neutral Words (Mean 23.33, SEM 2.57)		
Familiarity	Positive > Neutral	Positive Words (Mean 35.35, SEM 2.20)	2.936	0.029
		Neutral Words (Mean 23.33, SEM 2.57)		
Neutral Words	More Recollection than Familiarity Judgements	Recollection (Mean 35.35, SEM 2.20)	4.593	<0.001
		Familiarity (Mean 23.33, SEM 2.57)		

Figure 4.12 Word Recognition Remember/Know. Pairwise comparisons from the Recognition Type x Valence interaction. Figure key shows pairwise comparisons and significance levels. *(*p < .05,p<.005, ***p<.001)*. Bars show standard error.**



4.6.3.1 Summary of Word Recognition Remember/Know Behavioural Results

The interaction between recognition type and valence showed that for familiarity judgements there were greater percentages of negative and positive recognitions than there were for neutral recognitions. For neutral words only there were more subjective recollection judgements made than familiarity judgements.

4.6.4 Flanker Task

4.6.4.1 Accuracy

See Table 4.23 below for the means and SEMs for the Flanker task accuracy analysis. Significant effects and interactions are indicated.

Table 4.23 Flanker Task Accuracy. Means, SEMs for the analysis via the four-way mixed factorial glucoregulation x treatment x congruency x direction ANOVA. Significant effects and interactions are indicated (Gluc = Glucoregulation, Tr =Treatment, Cong = Congruency, Dir = Direction) (*P<0.001)**

Glucoregulation	N	Treatment	Congruency	Direction	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	11	Glucose	Congruent	Left	99.301	±	0.51	Cong ***
	11			Right	99.302	±	0.455	
	11		Incongruent	Left	95.573	±	1.288	
	11			Right	93.474	±	1.88	
	11		Neutral	Left	98.369	±	0.686	
	11			Right	98.835	±	0.645	
	11		NoGo	Left	89.511	±	2.412	
	11			Right	92.075	±	2.27	
	11	Placebo	Congruent	Left	98.835	±	0.728	
	11			Right	99.302	±	0.262	
	11		Incongruent	Left	94.64	±	1.52	
	11			Right	96.037	±	0.984	
	11		Neutral	Left	98.835	±	0.853	
	11			Right	99.068	±	0.64	
	11		NoGo	Left	91.842	±	1.623	
	11			Right	90.678	±	2.322	
Poorer Regulators	10	Glucose	Congruent	Left	99.231	±	0.535	
	10			Right	98.975	±	0.477	
	10		Incongruent	Left	93.59	±	1.35	
	10			Right	95.386	±	1.972	
	10		Neutral	Left	98.975	±	0.719	
	10			Right	98.719	±	0.676	
	10		NoGo	Left	91.539	±	2.53	
	10			Right	90.001	±	2.381	
	10	Placebo	Congruent	Left	99.232	±	0.763	
	10			Right	100	±	0.274	
	10		Incongruent	Left	93.591	±	1.594	
	10			Right	94.873	±	1.032	
	10		Neutral	Left	98.974	±	0.895	
	10			Right	98.719	±	0.672	
	10		NoGo	Left	91.539	±	1.702	
	10			Right	89.489	±	2.436	

The analysis of Flanker task data showed that the primary four-way glucoregulation x treatment x congruency x direction interaction was non-significant ($F(1.44,27.31) = 0.672$, $p = .423$, $r = 0.06$). See **Table 4.24** below for significant main effects and interactions.

Table 4.24 Flanker task accuracy ANOVA. F values, degrees of freedom, significance levels and effect sizes for interactions and main effects are shown.

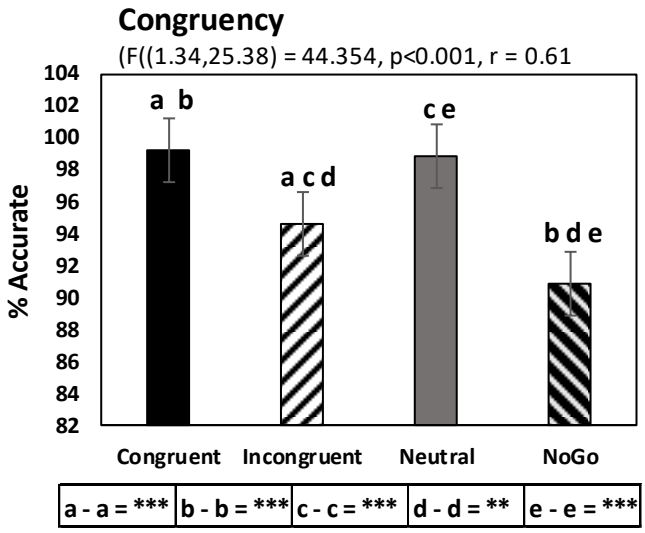
Main Effects/ Interactions	Df	F	p value	r
Congruency	(1.34,25.38)	44.354	<0.001	0.61

For the main effect of congruency (F(1.34,25.38) = 44.354, p<.001, r =0.61) (see Table 4.24 above) significant pairwise comparisons (see Table 4.25 and Figure 4.13 below) revealed that congruent Flanker responses were significantly more accurate than incongruent and NoGo responses. Neutral responses were more accurate than both incongruent and NoGo responses and incongruent responses were significantly more accurate than NoGo responses. In terms of mean accuracy congruent responses were greater and NoGo responses were least accurate.

Table 4.25 Flanker task analysis significant pairwise comparisons from the main effect of congruency. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition / Group	Pairwise Differences	Mean(SEM)	t(17)=	p Value
Congruency	Congruent more accurate than incongruent	Congruent (Mean 99.272, SEM 0.21)	7.856	<0.001
		Incongruent (Mean 94.65, SEM 0.62)		
Congruency	Congruent more accurate than NoGo	Congruent (Mean 99.272, SEM 0.21)	7.073	<0.001
		NoGo (Mean 90.83, SEM 1.27)		
Congruency	Incongruent less accurate than Neutral	Neutral (Mean 98.81, SEM 0.37)	7.506	<0.001
		Incongruent (Mean 94.65, SEM 0.62)		
Congruency	Incongruent more accurate than NoGo	Incongruent (Mean 94.65, SEM 0.62)	4.499	0.001
		NoGo (Mean 90.83, SEM 1.27)		
Congruency	Neutral more accurate than NoGo	Neutral (Mean 98.81, SEM 0.37)	6.848	<0.001
		NoGo (Mean 90.83, SEM 1.27)		

Figure 4.13 Flanker task accuracy. Pairwise comparison from the main effect of congruency. Figure key shows pairwise comparisons and significance levels. (p < .005, ***<.001*) Bars show standard error.**



4.6.4.2 Response Reaction Time

See **Table 4.26**

below for the means and SEMs for the Flanker task response reaction time analysis. Significant effects and interactions are indicated.

Table 4.26 Flanker task response reaction time. Means, SEMs for the analysis via the four-way mixed factorial glucoregulation x treatment x congruency x direction ANOVA. Significant effects and interactions are indicated (Gluc = Glucoregulation, Tr =Treatment, Cong = Congruency, Dir = Direction) (*p<0.05, ***P<0.001)

Glucoregulation	N	Treatment	Congruency	Direction	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	11	Glucose	Congruent	Left	440.47	±	20.60	
	11			Right	439.07	±	20.35	
	11		Incongruent	Left	508.46	±	18.77	
	11			Right	508.02	±	20.92	
	11		Neutral	Left	449.44	±	20.11	
	11			Right	441.27	±	20.54	
	11	Placebo	Congruent	Left	456.97	±	14.49	
	11			Right	449.86	±	14.56	
	11		Incongruent	Left	507.81	±	16.98	
	11			Right	504.45	±	21.30	
	11		Neutral	Left	458.18	±	16.89	Cong ***
	11			Right	454.95	±	17.69	
Poorer Regulators	10	Glucose	Congruent	Left	446.88	±	21.61	
	10			Right	446.34	±	21.34	Tr x Cong x Gluc *
	10		Incongruent	Left	507.75	±	19.69	
	10			Right	513.37	±	21.94	
	10		Neutral	Left	449.43	±	21.10	
	10			Right	440.75	±	21.54	
	10	Placebo	Congruent	Left	459.66	±	15.20	
	10			Right	459.50	±	15.27	
	10		Incongruent	Left	523.86	±	17.81	
	10			Right	546.61	±	22.34	
	10		Neutral	Left	462.58	±	17.72	
	10			Right	467.31	±	18.55	

The analysis of Flanker task response time data showed that the primary four-way glucoregulation x treatment x congruency x direction interaction was non-significant ($F(2,38) = 0.307$, $p = .738$, $r = 0.02$). See Table 4.27 below for significant main effects and interactions.

Table 4.27 Flanker task response reaction time ANOVA. F values, degrees of freedom, significance levels and effect sizes for interactions and main effects.

Main Effects/ Interactions	Df	F	p value	r
Congruency	(2,38)	139.153	<0.001	0.70
Glucoregulation x Treatment x Congruency	(2,38)	5.251	0.010	0.07

There was a significant glucoregulation x treatment x congruency interaction (F(2, 38) = 5.251, p = .010, r =0.07) (see Table 4.27 above and Table 4.28 below for interaction means and SEMs). Significant pairwise comparisons (see Table 4.29 Figure 4.14 below) revealed that the effect of congruency on the interaction showed that, for both better and poorer regulators and for both treatment conditions, incongruent responses were made more slowly in comparison to both congruent and neutral responses. There were no interaction effects of either glucoregulation or treatment.

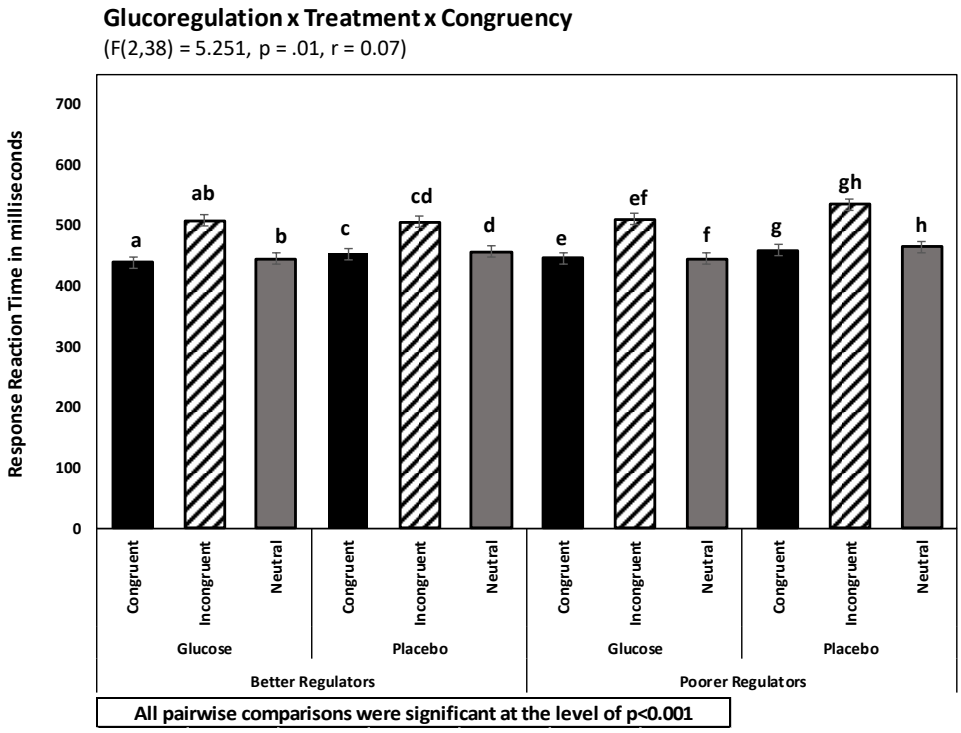
Table 4.28 Flanker Task response time analysis means and SEMs depicting the glucoregulation x treatment x congruency interaction.

Glucoregulation	Treatment	Congruency	Mean	±	SEM
Better Regulators	Glucose	Congruent	439.77	±	20.23
		Incongruent	508.24	±	19.04
		Neutral	445.35	±	19.90
	Placebo	Congruent	453.41	±	14.26
		Incongruent	506.13	±	18.26
		Neutral	456.56	±	16.69
Poorer Regulators	Placebo	Congruent	446.61	±	21.22
		Incongruent	510.56	±	19.97
		Neutral	445.09	±	20.87
	Placebo	Congruent	459.58	±	14.95
		Incongruent	535.23	±	19.15
		Neutral	464.94	±	17.51

Table 4.29 Flanker Task Response Reaction Time. Significant pairwise comparisons from the glucoregulation x treatment x congruency interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition / Group	Pairwise Differences	Mean(SEM)	t(18)=	p Value
Better Reguators, Glucose	Inongruent slower than congruent	Incongruent (Mean 508.24, SEM 19.04)	9.450	<0.001
		Congruent (Mean 439.77, SEM 20.23)		
Better Reguators, Glucose	Inongruent slower than neutral	Incongruent (Mean 508.24, SEM 19.04)	9.691	<0.001
		Neutral (Mean 445.35, SEM 19.90)		
Better Reguators, Placebo	Inongruent slower than congruent	Incongruent (Mean 506.13, SEM 18.26)	6.403	<0.001
		Congruent (Mean 453.41, SEM 14.26)		
Better Reguators, Placebo	Inongruent slower than neutral	Incongruent (Mean 506.13, SEM 18.26)	8.370	<0.001
		Neutral (Mean 456.56, SEM 16.69)		
Poorer Reguators, Glucose	Inongruent slower than congruent	Incongruent (Mean 510.56, SEM 19.97)	8.417	<0.001
		Congruent (Mean 446.61, SEM 21.22)		
Poorer Reguators, Glucose	Inongruent slower than neutral	Incongruent (Mean 510.56, SEM 19.97)	9.621	<0.001
		Neutral (Mean 445.09, SEM 20.87)		
Poorer Reguators, Placebo	Inongruent slower than congruent	Incongruent (Mean 535.23, SEM 19.15)	8.762	<0.001
		Congruent (Mean 459.58, SEM 14.95)		
Poorer Reguators, Placebo	Inongruent slower than neutral	Incongruent (Mean 535.23, SEM 19.15)	8.008	<0.001
		Neutral (Mean 464.94, SEM 17.51)		

Figure 4.14 Flanker Task Response Reaction Time. Pairwise comparisons from glucoregulation x treatment x congruency interaction. Figure key shows pairwise comparisons and significance levels. All comparisons were significant at p<.001. Bars show standard error.



4.6.4.2.1 Summary of Flanker Task Results

In terms of accuracy, the main effect of congruency showed responses to congruent flanker arrays were more accurate than incongruent and NoGo responses. Neutral responses were more accurate than both incongruent and NoGo responses and incongruent responses were more accurate than NoGo responses. In terms of mean accuracy congruent responses were greater and NoGo responses were least accurate.

In terms of response reaction times, the glucoregulation x treatment x congruency interaction showed both better and poorer regulators and following both glucose and placebo, making slower responses to incongruent compared to both congruent and neutral Flanker arrays.

4.7 ERP Results

4.7.1 Encoding Phase

4.7.1.1 Encoding P1

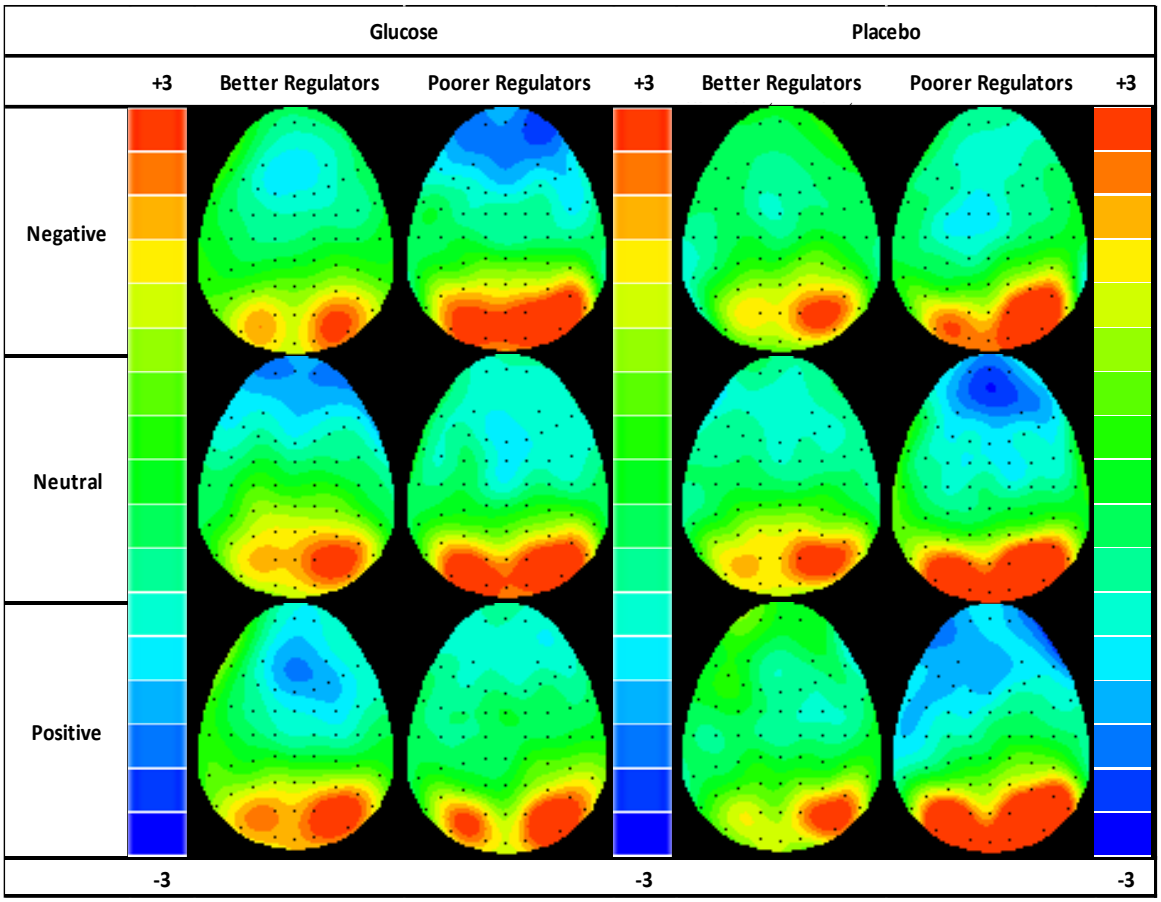
See Appendix 4.3 for the means and SEMs for the P1 component amplitude analysis. Significant effects and interactions are indicated.

For the analysis of P1 component in the 50 – 170ms time window the primary five-way glucoregulation x treatment x region x valence x hemisphere interaction was non-significant ($F(2.90, 46.43) = 1.266$, $p = .297$). Significant main effects and interactions are shown below in Table 4.30. Only significant higher order interactions are reported in the text. Topographical maps representing the P1 component can be seen in Figure 4.15 below.

Table 4.30 Encoding Phase P1 Component. Significant main effects and interactions from the five-way glucoregulation x treatment x valence x region x hemisphere mixed factorial ANOVA conducted on encoding data in the 50 - 170 ms time window. ANOVA F values, degrees of freedom, significance levels and effect sizes are shown.

Main Effect/ Interaction	df	F	p value	r
Region x hemisphere	(1.91,30.62)	6.739	.004	0.12
Region	(1,16)	39.556	<.001	0.59
Hemisphere	(1.57, 25.07)	7.595	.005	0.12

Figure 4.15 Encoding Phase P1 Component. ERP topographies of grand average data across the 50-170 ms time window. The colour scale shows amplitude ranges from positive (red) to negative (blue) inflections from +3 to -3 microvolts.



The two-way region x hemisphere interaction was significant (F(1.91,30.62) = 6.739, p = .004, r =0.12) (see Table 4.30 above and Table 4.31 below for interaction means and SEMs). Regional effects on the interaction showed that the P1 amplitude was greater for left hemisphere, midline and right hemisphere electrodes at the posterior region compared to anterior electrodes. Interaction

hemisphere effects revealed that left anterior were greater than right anterior amplitudes and right posterior amplitudes were greater than both midline and right posterior amplitudes. The interaction P1 amplitude was maximal at the right posterior electrode. The See Table 4.32 and Figure 4.16 below for significant pairwise comparisons.

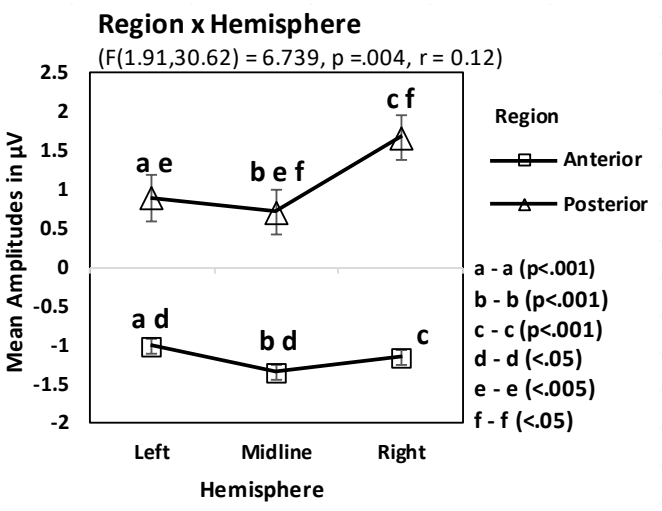
Table 4.31 Encoding Phase P1 Component. Amplitude means and SEMs depicting the region x hemisphere interaction.

Region	Hemisphere	Mean	±	SEM
			±	
Anterior	Left	-1.012	±	0.214
	Midline	-1.356	±	0.271
	Right	-1.156	±	0.282
Posterior	Left	0.892	±	0.249
	Midline	0.713	±	0.203
	Right	1.672	±	0.209

Table 4.32 Encoding Phase P1 Component. Significant pairwise comparisons from the Region x Hemisphere interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition / Group	Pairwise Differences	Mean(SEM)	t(16)=	p Value
Left Hemisphere	Posterior > Anterior Region	Posterior (Mean 0.892, SEM 0.249)	4.577	<0.001
		Anterior (Mean -1.012, SEM 0.214)		
Midline Hemisphere	Posterior > Anterior Region	Posterior (Mean 0.713, SEM 0.203)	6.103	<0.001
		Anterior (Mean -1.356, SEM 0.271)		
Right Hemisphere	Posterior > Anterior Region	Posterior (Mean 1.672, SEM 0.209)	6.782	<0.001
		Anterior (Mean -1.156, SEM 0.282)		
Anterior Region	Left > Midline	Left (Mean -1.012, SEM 0.214)	3.071	0.022
		Midline (Mean -1.356, SEM 0.271)		
Posterior Region	Right > Midline	Right (Mean 1.672, SEM 0.209)	4.655	0.001
		Midline (Mean 0.713, SEM 0.242)		
Posterior Region	Right > Left	Right (Mean 1.672, SEM 0.209)	3.059	0.023
		Left (Mean 0.892, SEM 0.249)		

Figure 4.16 Encoding Phase P1 Component. Pairwise comparisons from the Region x Hemisphere interaction. See figure key for significance levels. Bars show standard error.



4.7.1.2 N1 negative going component.

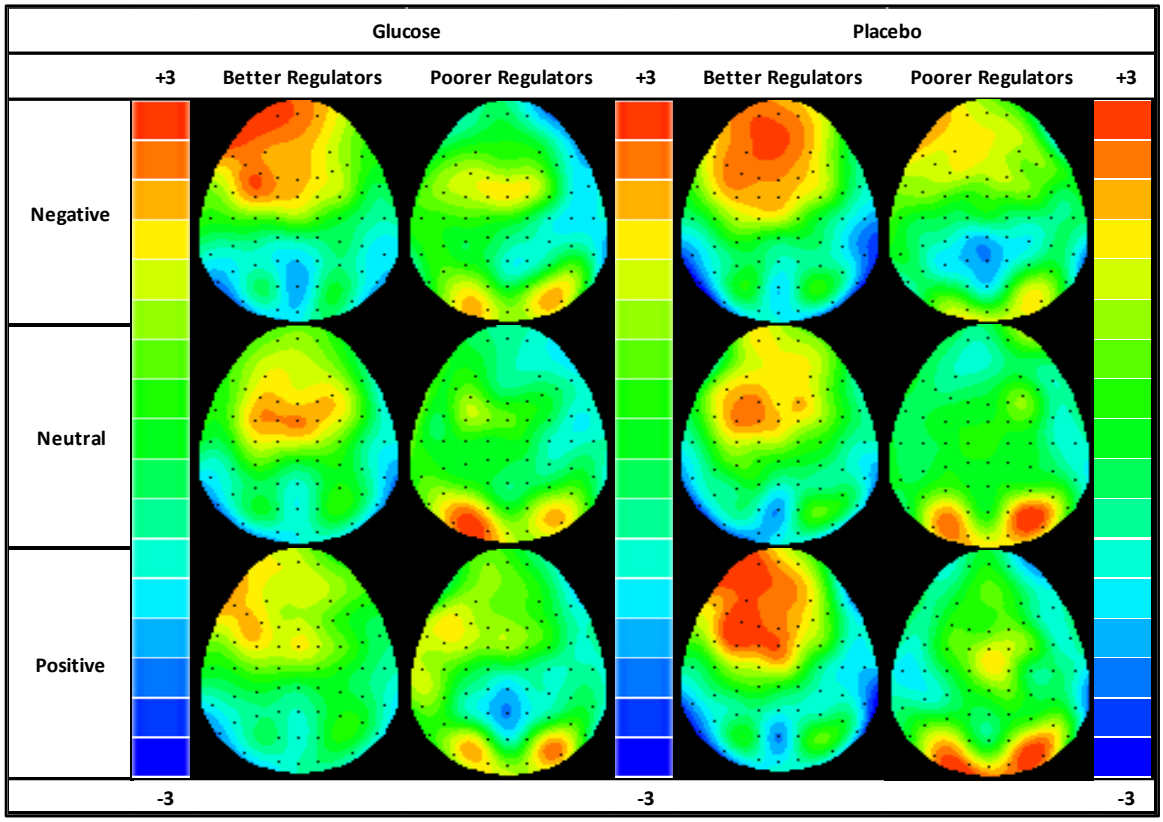
See Appendix 4.4 for the means and SEMs for the N1 component amplitude analysis. Significant effects and interactions are indicated.

For the analysis of N1 component data in the 165 – 220ms time window the primary five-way glucoregulation x treatment x region x valence x hemisphere interaction was non-significant (F(2.57, 41.18) = 2.711, p = .119, r = 0.04). Significant and main effects and interactions are shown below in Table 4.33. Topographical maps representing the N1 component can be seen in Figure 4.17 below.

Table 4.33 Encoding Phase N1 Component. Main effects and interactions from the five-way glucoregulation x treatment x valence x region x hemisphere ANOVA conducted on encoding data in the 165 - 220 ms time window. ANOVA F values, degrees of freedom, significance levels and effect sizes are shown.

Main Effect/ Interaction	df	F	p value	R
Region x hemisphere	(1.76,28.23)	5.377	0.013	0.10

Figure 4.17 Encoding Phase N1 Component. ERP topographies of grand average data across the 165-220 ms time window. The colour scale shows amplitude ranges from positive (red) to negative (blue) inflections from +3 to -3 microvolts.

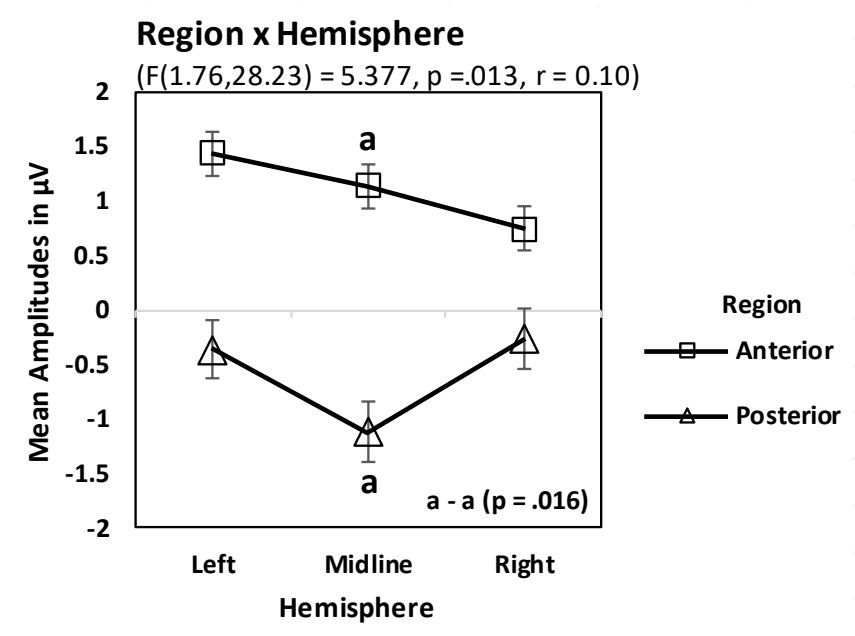


The two-way region x hemisphere interaction (F(1.76, 28.23) = 5.377, p = .013, r = 0.10), (see Table 4.33 above and Table 4.34 below for interaction means and SEMs), showed that the midline posterior N1 amplitude (Mean -1.122, SEM 0.431) was greater than at midline anterior (Mean 1.141, SEM 0.485) (t(16) = 2.700, p = .016), see Figure 4.18 below. The interaction N1 amplitude was maximal at the midline posterior electrode.

Table 4.34 Encoding Phase N1 Component. Amplitude means and SEMs depicting the region x hemisphere interaction.

Region	Hemisphere	Mean	±	SEM
Anterior	Left	1.436	±	0.48
	Midline	1.141	±	0.485
	Right	0.747	±	0.491
Posterior	Left	-0.361	±	0.519
	Midline	-1.122	±	0.431
	Right	-0.266	±	0.617

Figure 4.18 Encoding Phase N1 Component. Pairwise comparisons from the Region x Hemisphere interaction. See figure key for significance levels. Bars show standard error.



4.7.1.3 P3 Component

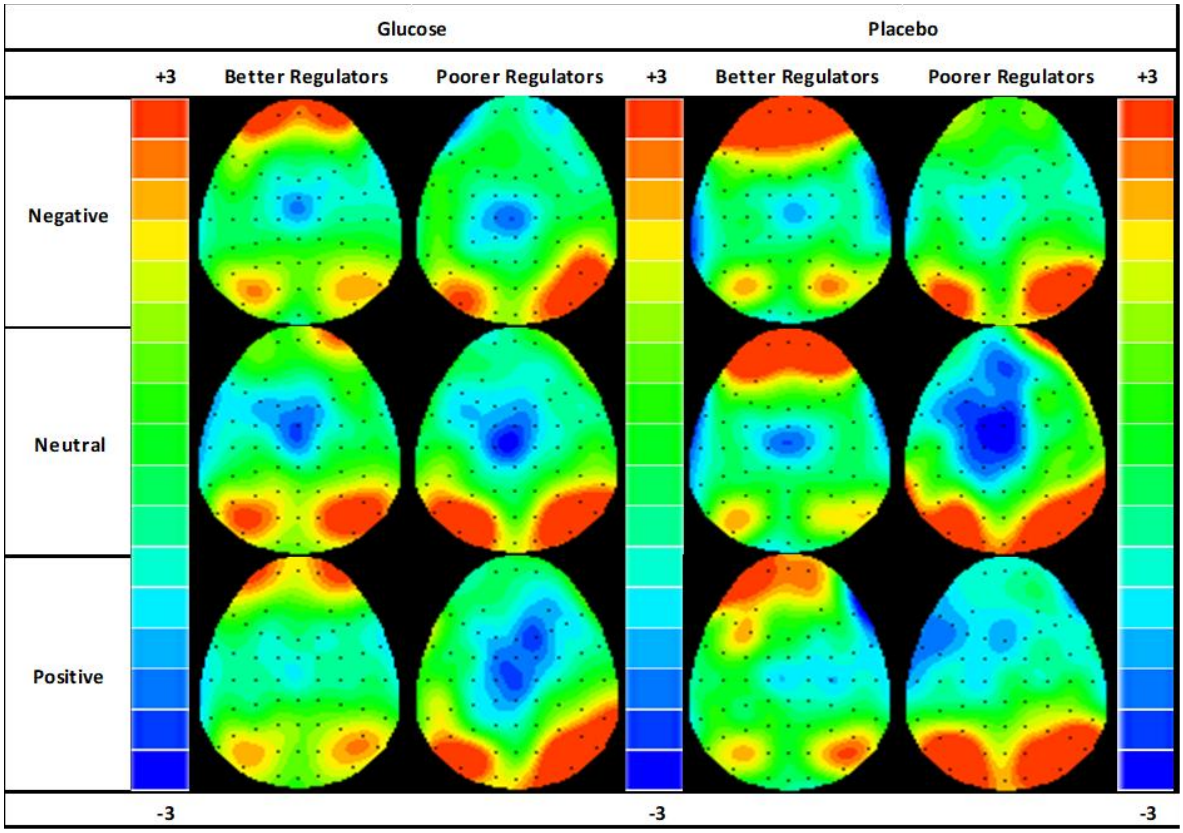
Appendix 4.5See Appendix 4.5 for the means and SEMs for the P3 component amplitude analysis. Significant effects and interactions are indicated.

For the analysis of P3 component data in the 300 – 500ms time window the primary five-way treatment x glucoregulation x region x valence x hemisphere was non-significant (F(2.82, 45.10) = 1.573, p = .211, r = 0.045). Significant main effects and interactions are shown below in Table 4.35. Only significant higher order interactions are reported in the text. Topographical maps representing the P3 component can be seen in Figure 4.19 below.

Table 4.35 Encoding Phase P3 Component. Significant main effects and interactions from the five-way glucoregulation x treatment x valence x region x hemisphere ANOVA conducted on encoding data in the 300 - 500 ms time window. ANOVA F values, degrees of freedom, significance levels and effect sizes are shown.

Main Effect/ Interaction	df	F	p value	r
Glucoregulation x treatment x region x hemisphere	(1.92, 30.71)	3.671	.039	0.05
Region x valence x hemisphere	(2.78, 44.53)	6.315	.001	0.07
Region x hemisphere	(1.67, 26.77)	4.912	.020	0.09
Region	(1,16)	8.023	.012	0.34
Hemisphere	(1.89, 30.21)	8.756	.001	0.18

Figure 4.19 Encoding Phase P3 Component. ERP topographies of grand average data across the 300-500 ms time window. The colour scale shows amplitude ranges from positive (red) to negative (blue) inflections from +3 to -3 microvolts.



There was a significant four-way glucoregulation x treatment x region x hemisphere interaction (F(1.92,30.71) = 3.671, p = .039, r = 0.05), see Table 4.35 above and Table 4.36 below for interaction

means and SEMs. Pairwise comparisons for this interaction can be found in Table 4.37 and Figure 4.20. Effects of glucoregulation on the interaction showed that better regulators had enhanced left anterior P3 than did poorer regulators following placebo. Interaction treatment effects revealed that for better glucoregulators the left anterior P3 amplitude was lesser following glucose than following placebo. Regional effects on the interaction showed that all posterior P3 amplitudes were greater than anterior P3 amplitudes following glucose. Poorer regulators had enhanced right posterior P3 amplitudes compared to right anterior P3 amplitudes following glucose and following placebo enhanced left and right posterior P3 amplitudes relative to left and right anterior amplitudes. In terms of hemisphere effects on the interaction, these did not reveal any meaningful outcomes, but they can be seen in the table and figure. The maximal P3 amplitude was elicited by poorer regulators after glucose at the right posterior electrode.

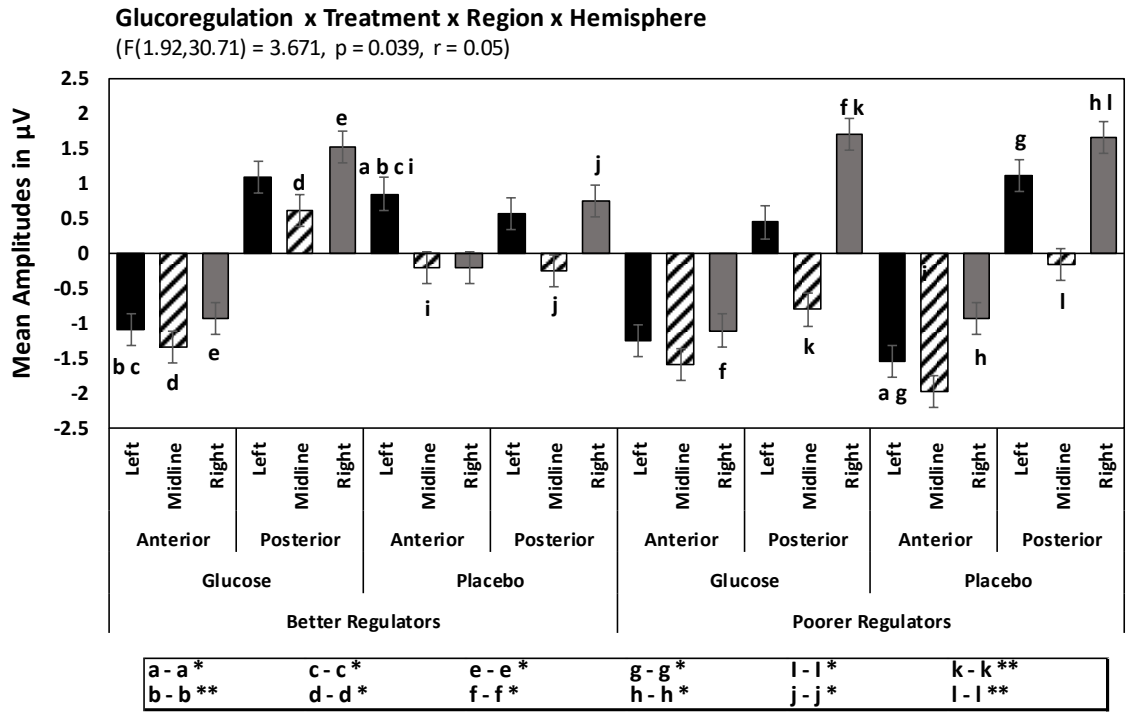
Table 4.36 Encoding Phase P3 Component. Amplitude means and SEMs depicting the glucoregulation x treatment x region x hemisphere interaction.

Glucoregulation	Treatment	Region	Hemisphere	Mean	±	SEM
Better Regulators	Glucose	Anterior	Left	-1.094	±	0.529
			Midline	-1.334	±	0.619
			Right	-0.933	±	0.528
		Posterior	Left	1.091	±	0.468
			Midline	0.615	±	0.462
			Right	1.525	±	0.482
	Placebo	Anterior	Left	0.857	±	0.606
			Midline	-0.207	±	0.542
			Right	-0.202	±	0.455
		Posterior	Left	0.58	±	0.465
			Midline	-0.252	±	0.609
			Right	0.761	±	0.6
Poorer Regulators	Glucose	Anterior	Left	-1.24	±	0.663
			Midline	-1.58	±	0.776
			Right	-1.099	±	0.662
		Posterior	Left	0.45	±	0.586
			Midline	-0.8	±	0.579
			Right	1.715	±	0.604
	Placebo	Anterior	Left	-1.539	±	0.76
			Midline	-1.975	±	0.679
			Right	-0.935	±	0.57
		Posterior	Left	1.127	±	0.583
			Midline	-0.155	±	0.764
			Right	1.665	±	0.753

Table 4.37 Encoding Phase P3 Component. Significant pairwise comparisons from the Glucoregulation x Treatment x Region x Hemisphere interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition / Group	Pairwise Differences	Mean(SEM)	t(16)=	p Value
Placebo, Anterior Region, Left Hemisphere	Better > Poorer	Better (Mean 0.857, SEM 0.606)	2.465	0.025
		Poorer (Mean -1.539, SEM 0.760)		
Better Regulators, Anterior Region, Left Hemisphere	Placebo > Glucose	Glucose (Mean -1.094, SEM 0.529)	4.041	0.001
		Placebo (Mean 0.857, SEM 0.606)		
Better Regulators, Glucose, Left Hemisphere	Posterior > Anterior Region	Posterior (Mean 1.1091, SEM 0.468)	2.351	0.032
		Anterior (Mean -1.094, SEM 0.529)		
Better Regulators, Glucose, Midline Hemisphere	Posterior > Anterior Region	Posterior (Mean 0.615, SEM 0.462)	2.409	0.028
		Anterior (Mean -1.334, SEM 0.619)		
Better Regulators, Glucose, Right Hemisphere	Posterior > Anterior Region	Posterior (Mean 1.525, SEM 0.482)	3.027	0.008
		Anterior (Mean -0.933, SEM 0.528)		
Poorer Regulators, Glucose, Right Hemisphere	Posterior > Anterior Region	Posterior (Mean 1.715, SEM 0.604)	2.764	0.014
		Anterior (Mean -1.099, SEM 0.632)		
Poorer Regulators, Placebo, Left Hemisphere	Posterior > Anterior Region	Posterior (Mean 1.127, SEM 0.583)	2.308	0.035
		Anterior (Mean -1.539, SEM 0.760)		
Poorer Regulators, Placebo, Right Hemisphere	Posterior > Anterior Region	Posterior (Mean 1.665, SEM 0.753)	2.317	0.034
		Anterior (Mean -0.935, SEM 0.570)		
Better Regulators, Placebo, Anterior Region	Left > Midline	Left (Mean 0.857, SEM 0.606)	2.764	0.041
		Midline (Mean -0.207, SEM 0.542)		
Better Regulators, Placebo, Posterior Region	Right > Midline	Right (Mean 0.761, SEM 0.600)	2.687	0.048
		Midline (Mean -0.252, SEM 0.609)		
Poorer Regulators, Glucose, Posterior Region	Right > Midline	Right (Mean 1.715, SEM 0.604)	4.397	0.001
		Midline (Mean -0.800, SEM 0.579)		
Poorer Regulators, Placebo, Posterior Region	Right > Midline	Right (Mean 1.665, SEM 0.753)	4.858	0.004
		Midline (Mean -0.155, SEM 0.764)		

Figure 4.20 Encoding Phase P3 Component. Pairwise comparison from the glucoregulation x treatment x region x hemisphere interaction. Figure key shows pairwise comparisons and significance levels. (*p<.05,p < .005) Bars show standard error.**



There was a three-way region x valence x hemisphere interaction (F(2.78,44.53) =6.315, p = 001, r = 0.07) (see Table 4.35 above and Table 4.38 below for interaction means and SEMs). Pairwise comparisons for this interaction can be found in Table 4.39 and Figure 4.21 below. Regional effects on the interaction showed that posterior P3 amplitudes were greater than anterior P3 amplitudes, effects of valence showed greater right posterior P3 amplitudes for negative, neutral, and positive words, with a maximal P3 at the right posterior electrode elicited by negative words.

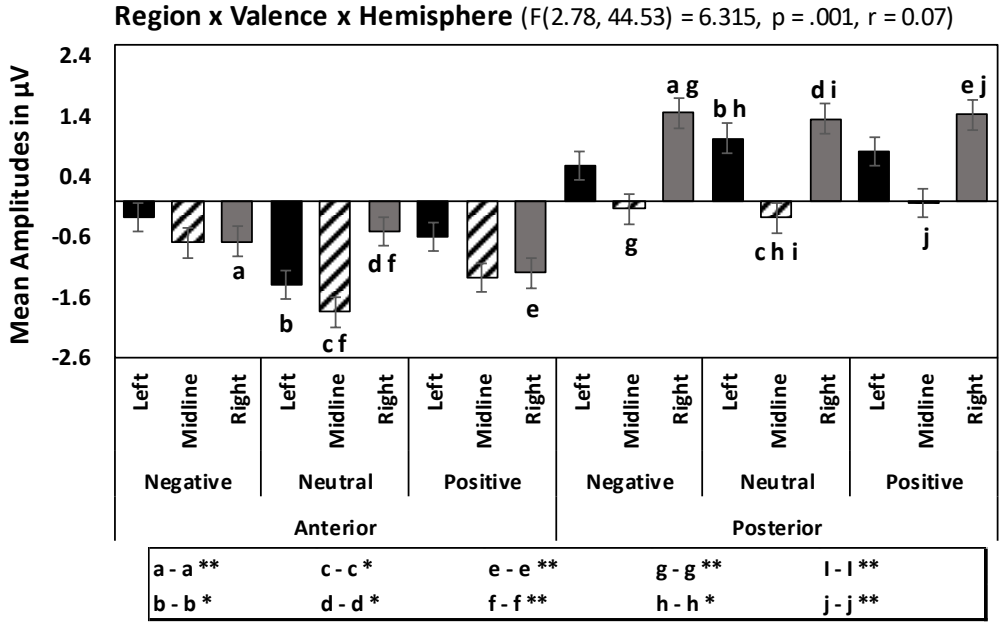
Table 4.38 Encoding Phase P3 Component. Amplitude means and SEMs depicting the region x valence x hemisphere interaction.

Region	Valence	Hemisphere	Mean	±	SEM
Anterior	Negative	Left	-0.264	±	0.464
		Midline	-0.695	±	0.571
		Right	-0.672	±	0.451
	Neutral	Left	-1.395	±	0.506
		Midline	-1.848	±	0.468
		Right	-0.508	±	0.39
	Positive	Left	-0.602	±	0.507
		Midline	-1.278	±	0.413
		Right	-1.198	±	0.426
Posterior	Negative	Left	0.58	±	0.407
		Midline	-0.135	±	0.432
		Right	1.458	±	0.347
	Neutral	Left	1.039	±	0.412
		Midline	-0.282	±	0.414
		Right	1.365	±	0.496
	Positive	Left	0.817	±	0.372
		Midline	-0.027	±	0.419
		Right	1.427	±	0.486

Table 4.39 Encoding Phase P3 Component. Significant pairwise comparisons from the Region x Valence x Hemisphere interaction. Pairwise differences, means and SEM, t-values, degrees of freedom and p-values are shown.

Condition / Group	Pairwise Differences	Mean(SEM)	t(15)=	p Value
Negative Words, Right Hemisphere	Posterior > Anterior Region	Posterior (Mean 1.458, SEM 0.347) Anterior (Mean -0.672, SEM 0.451)	3.646	0.002
Neutral Words, Left Hemisphere	Posterior > Anterior Region	Posterior (Mean 1.039, SEM 0.412) Anterior (Mean -1.395, SEM 0.506)	3.118	0.007
Neutral Words, Midline Hemisphere	Posterior > Anterior Region	Posterior (Mean -0.282, SEM 0.414) Anterior (Mean -1.848, SEM 0.468)	2.417	0.028
Neutral Words, Right Hemisphere	Posterior > Anterior Region	Posterior (Mean 1.365, SEM 0.496) Anterior (Mean -0.508, SEM 0.390)	2.442	0.027
Positive Words, Right Hemisphere	Posterior > Anterior Region	Posterior (Mean 1.427, SEM 0.486) Anterior (Mean -1.198, SEM 0.426)	3.849	0.001
Anterior Region, Neutral Words	Right > Midline	Right (Mean -0.508, SEM 0.390) Midline (Mean -1.848, SEM 0.468)	4.340	0.002
Posterior Region, Negative Words	Right > Midline	Right (Mean 1.458, SEM 0.347) Midline (Mean -0.135, SEM 0.432)	4.781	0.001
Posterior Region, Neutral Words	Left > Midline	Left (Mean 1.039, SEM 0.412) Midline (Mean -0.282, SEM 0.414)	3.807	0.005
Posterior Region, Neutral Words	Right > Midline	Right (Mean 1.365, SEM 0.496) Midline (Mean -0.282, SEM 0.414)	4.138	0.002
Posterior Region, Positive Words	Right > Midline	Right (Mean 1.427, SEM 0.486) Midline (Mean -0.027, SEM 0.486)	4.242	0.002

Figure 4.21 Encoding Phase P3 Component. Pairwise comparison from the region x valence x hemisphere interaction. Figure key shows pairwise comparisons and significance levels. (*p<.05,p < .005) Bars show standard error.**



4.7.1.4 Late positive component

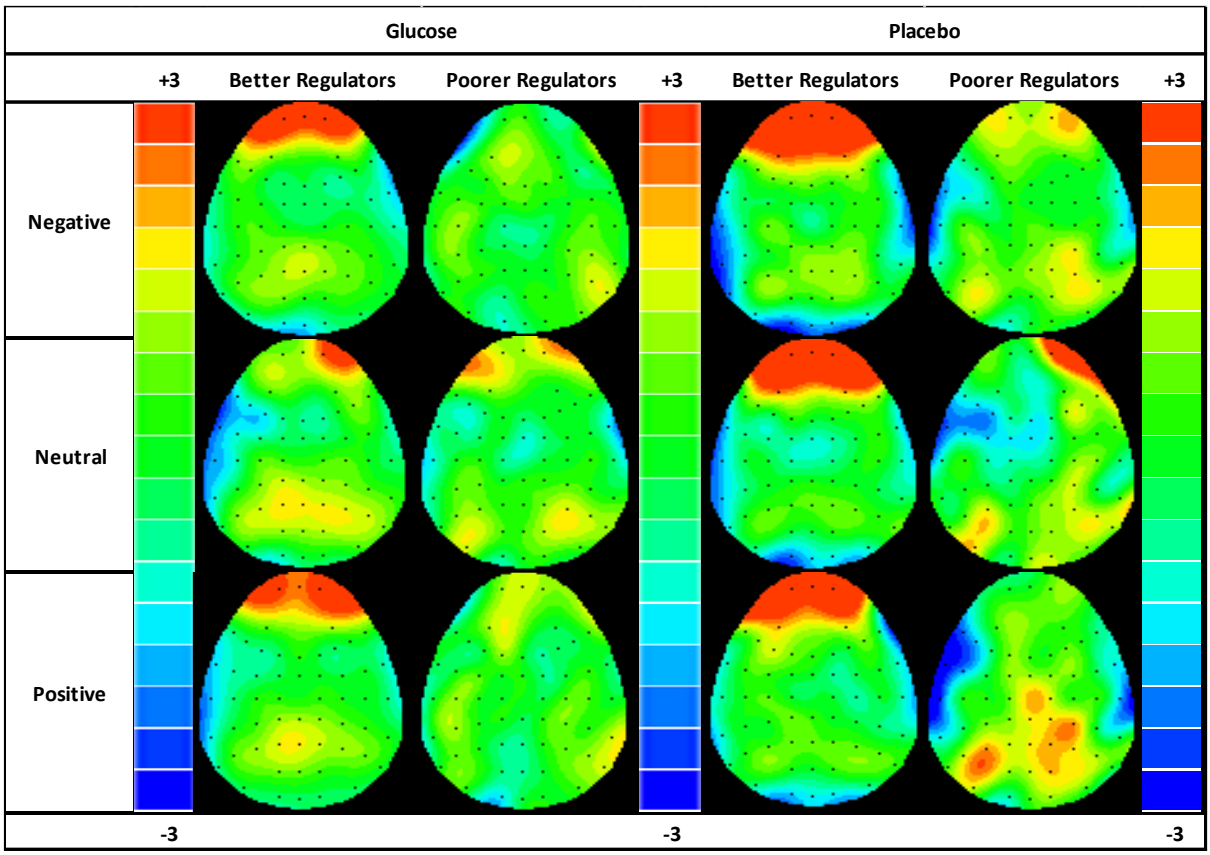
See Appendix 4.6 for the means and SEMs for the P3 component amplitude analysis. Significant effects and interactions are indicated.

For the analysis of positive going late positive component data for the 400 – 800ms time window the primary five-way treatment x glucoregulation x region x valence x hemisphere was non-significant (F(2.94,47.08) = 1.616, p = .199, r = 0.151). Significant main effects and interactions are shown below in Table 4.40. Only significant higher order interactions are reported in the text. Topographical maps representing the LPC component can be seen in Figure 4.22 below.

Table 4.40 Encoding Late Positive Component. significant main effects and interactions from the five-way glucoregulation x treatment x valence x region x hemisphere multi factorial ANOVA conducted on encoding data in the 400 - 800 ms time window. ANOVA F values, degrees of freedom, significance levels and effect sizes are shown.

Main Effect/ Interaction	df	F	p value	r
Glucoregulation x treatment x region	(1,16)	5.177	.037	0.16
Region x valence x hemisphere	(3.29, 52.71)	5.240	.002	0.06
Treatment x valence	(1.93,30.91)	4.139	.027	0.07

Figure 4.22 Encoding Late Positive Component. ERP topographies of grand average encoding data across the 400-800 ms time window. The colour scale shows amplitude ranges from positive (red) to negative (blue) inflections from +3 to -3 microvolts.

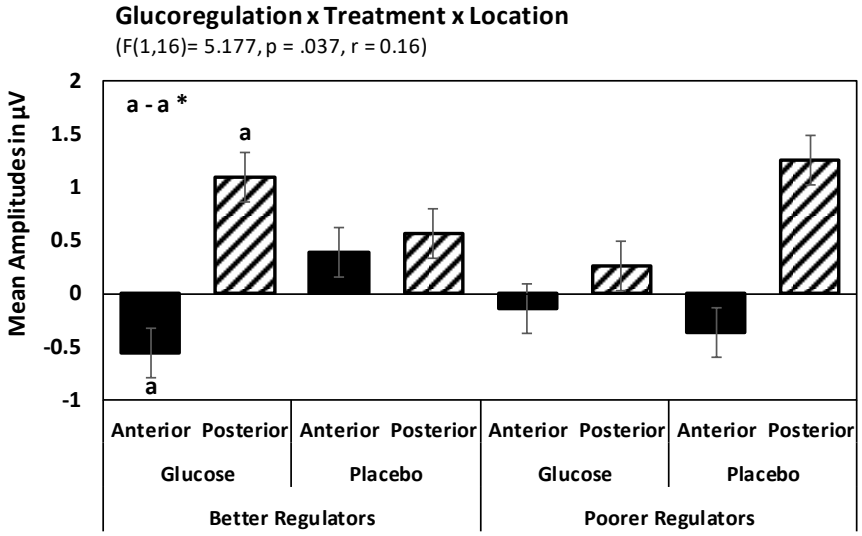


There was a three-way glucoregulation x treatment x region interaction ($F(1,16)= 5.177$, $p = .037$, $r = 0.16$) (see Table **4.35** and **Table 4.40** above and Table 4.41 below for interaction means and SEMs). Interaction effects of region revealed that following glucose ingestion better regulators had a greater LPC amplitude at the posterior region (Mean 1.089, SEM 0.378) relative to the anterior region (Mean -0.565, SEM 0.432) ($t(16) = 2.380$, $p = .030$). There were no significant effects of glucoregulation or treatment on the interaction. The maximal LPC amplitude for the interaction was elicited by poorer regulators following the placebo treatment See Figure 4.23 below.

Table 4.41 Encoding Late Positive Component. amplitude means and SEMs depicting the glucoregulation x treatment x region interaction.

Glucoregulation	Treatment	Region	Mean	±	SEM
Better Regulators	Glucose	Anterior	-0.565	±	0.432
		Posterior	1.089	±	0.378
	Placebo	Anterior	0.38	±	0.465
		Posterior	0.557	±	0.461
Poorer Regulators	Glucose	Anterior	-0.144	±	0.541
		Posterior	0.264	±	0.474
	Placebo	Anterior	-0.369	±	0.583
		Posterior	1.261	±	0.578

Figure 4.23 Encoding Late Positive Component. Pairwise comparison from the Glucoregulation x Treatment x Region interaction. Figure key shows pairwise comparisons and significance levels. Bars show standard error.



There was a three-way region x valence x hemisphere interaction (F(3.29,52.71) = 5.240, p = .002, r = 0.06), see Table 4.40 above and Table 4.42 below for interaction means and SEMs. Regional effects of the interaction revealed that the left and midline hemisphere LPC in response to neutral words was greater at the posterior than the anterior region. In terms of valence effects, the response to positive words elicited greater LPC amplitudes than did neutral words at the left anterior. The effect of hemisphere on the interaction revealed greater right compared to midline anterior LPC amplitude in response to neutral words. LPC amplitudes were highest at the right posterior position in response to neutral words. See Table 4.43 and Figure 4.24 below for significant pairwise comparisons.

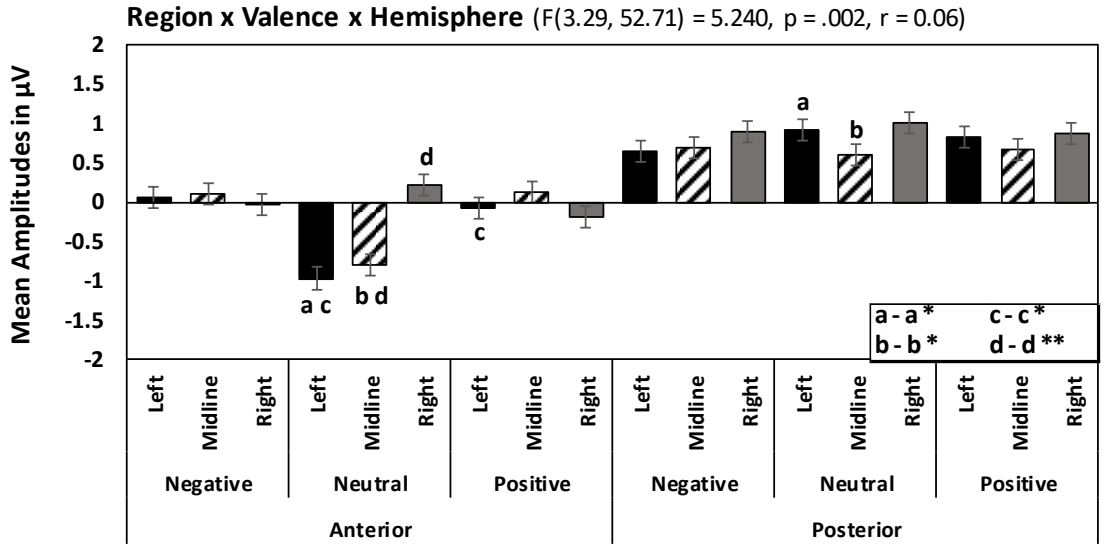
Table 4.42 Encoding Late Positive Component. Amplitude means and SEMs depicting the region x valence x hemisphere interaction.

Region	Valence	Hemisphere	Mean	±	SEM
Anterior	Negative	Left	0.054	±	0.401
		Midline	0.114	±	0.529
		Right	-0.03	±	0.453
	Neutral	Left	-0.969	±	0.465
		Midline	-0.796	±	0.39
		Right	0.209	±	0.405
	Positive	Left	-0.084	±	0.464
		Midline	0.126	±	0.408
		Right	-0.195	±	0.41
Posterior	Negative	Left	0.653	±	0.37
		Midline	0.686	±	0.385
		Right	0.891	±	0.306
	Neutral	Left	0.922	±	0.354
		Midline	0.607	±	0.326
		Right	1.018	±	0.436
	Positive	Left	0.82	±	0.34
		Midline	0.672	±	0.362
		Right	0.867	±	0.404

Table 4.43 Encoding Late Positive Component. Significant pairwise comparisons from the Region x Valence x Hemisphere interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition / Group	Pairwise Differences	Mean(SEM)	t(16)=	p Value
Neutral Words, Left Hemisphere	Posterior > Anterior Region	Posterior (Mean 0.922, SEM 0.354)	2.729	0.015
		Anterior (Mean -0.969, SEM 0.465)		
Neutral Words, Midline Hemisphere	Posterior > Anterior Region	Posterior (Mean 0.607, SEM 0.326)	2.562	0.021
		Anterior (Mean -0.796, SEM 0.390)		
Anterior Region, Left Hemisphere	Positive Words > Neutral Words	Positive (Mean -0.084, SEM 0.464)	2.921	0.030
		Neutral (Mean -0.969, SEM 0.465)		
Anterior Region, Neutral Words	Right > Midline	Right (Mean 0.209, SEM 0.405)	3.864	0.001
		Midline (Mean -0.796, SEM 0.390)		

Figure 4.24 Encoding Late Positive Component. Pairwise comparison from the region x valence x hemisphere interaction. Figure key shows pairwise comparisons and significance levels. (*p<.05,p < .005). Bars show standard error.**

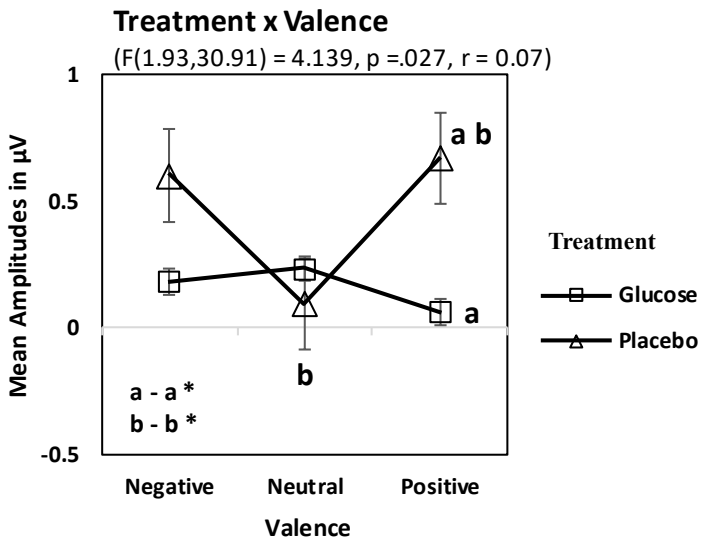


For the two-way treatment x valence interaction (F(1.93,30.91) = 4.139, p = .027, r = 0.07), (see Table 4.40 above Table 4.44 below for interaction means and SEMs), pairwise comparisons revealed that for presentation of positive words, the LPC amplitude was smaller following glucose than following placebo consumption (t(15)=2.643, p = .018). Also, the LPC amplitude was greater for positive relative to neutral words following placebo, (t(15)=3.021, p = .024). Highest LPC amplitudes were seen following placebo and positive words. See **Figure 4.25** below.

Table 4.44 Encoding Late Positive Component. Amplitude means and SEMs depicting the treatment x valence interaction.

Treatment	Valence	Mean	±	SEM
Glucose	Negative	0.184	±	0.196
	Neutral	0.235	±	0.195
	Positive	0.063	±	0.200
Placebo	Negative	0.605	±	0.278
	Neutral	0.095	±	0.211
	Positive	0.672	±	0.193

Figure 4.25 Encoding Late Positive Component. Pairwise comparison from the treatment x valence interaction. Figure key shows pairwise comparisons and significance levels. (*p<.05). Bars show standard error.



4.7.1.4.1 Summary of Encoding Phase ERP Data Results

The P1 component in the 50 – 170ms time window identified an interaction between region and hemisphere showed greater posterior amplitudes than at anterior electrodes. The P1 was maximal at the right posterior electrode.

For N1 component in the 165 – 220ms time window there was a region x hemisphere interaction showed amplitudes were maximal at the midline posterior electrode.

The P3 component across the 300 – 500ms time window identified an interaction between glucoregulation, treatment, region, and hemisphere. Which showed that compared to poorer regulators, better regulators were seen to have enhanced left anterior P3 amplitudes than poorer regulators. For poorer regulators only, the right posterior P3 was greater than the right anterior P3 following glucose, which may support the notion that poorer regulators are benefitting more from the glucose dose. Interaction effects of valence showed that P3 amplitudes were maximal following negative word encoding at the right posterior electrode.

Assessed across the 400 – 800ms time window an interaction between glucoregulation, treatment and region showed that, posterior LPC amplitudes were significantly greater than anterior amplitudes for better regulators and following glucose. The interaction between region and valence showed that the left anterior LPC was greater in response to positive words relative to neutral words. In terms of the treatment x valence interaction, positive words evoked lower LPC amplitudes following glucose compared to placebo.

4.7.2 Word Recognition Phase

4.7.2.1 FN400 component 300-500 ms Old/New Analysis

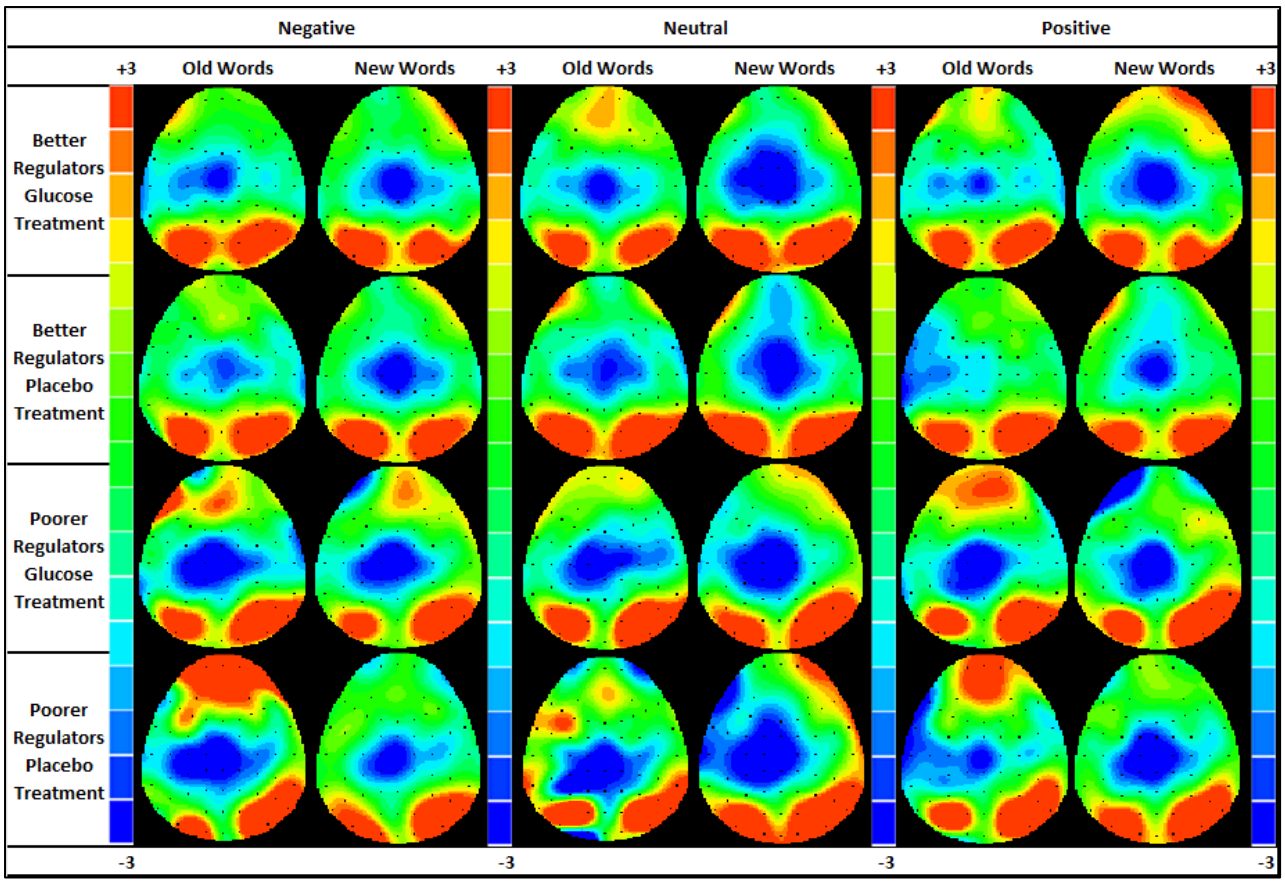
See Appendix 4.7 for the means and SEM for the ERP data for correct recognitions of old words and correct rejections of new words in word recognition phase the word recognition phase FN400 component analysis. Significant effects and interactions are indicated.

For the analysis of FN400 component data in the 300 – 500ms time window, the primary six-way glucoregulation x treatment x region x word type x valence x hemisphere interaction was non-significant (F(3.41,51.09) = 01.144, p = .343, r = 0.02). Significant effects and interactions are shown below in Table 4.45. Only significant higher order interactions are reported in the text. Topographical maps representing the FN400 component can be seen in Figure 4.26 below.

Table 4.45 Word Recognition Old/New FN400 component. Significant main effects and interactions from the six-way glucoregulation x treatment x word type x valence x region x hemisphere mixed factorial ANOVA conducted on recognition data in the 300 - 500 ms time window. ANOVA F values, degrees of freedom, significance levels and effect sizes are shown.

Main Effect/ Interaction	df	F	p value	r
Region x Word Type x Hemisphere	(1.79,26.85)	4.638	0.022	0.03
Region x Valence x Word Type	(1.83, 27.43)	3.441	0.05	0.08
Region x Hemisphere	(1.60, 24.05)	8.419	0.003	0.14
Valence x Word Type	(1.52, 22.76)	8.159	0.004	0.08
Region x Valence	(1.68,25.16)	4.696	0.023	0.07
Valence	(1.41,21.12)	4.480	0.035	0.06
Hemisphere	(1.86,27.83)	27.415	<0.001	0.30

Figure 4.26 Word Recognition Old/New FN400 component. ERP topographies of grand average data across the 300-500 ms time window. The colour scale shows amplitude ranges from positive (red) to negative (blue) inflections from +3 to -3 microvolts.



There was a three-way region x word type x hemisphere interaction ($F(1.79,26.85) = 4.638$, $p = .022$, $r = 0.03$ (see Table 4.45 above and Table 4.46 below for interaction means and SEMs). Significant pairwise comparisons can be found below in Table 4.47 and Figure 4.27. There were no regional interaction effects. The effect of word type on the interaction revealed higher right anterior FN400 amplitudes for new words relative to old words. There were several effects of hemisphere on the interaction, these can be seen below in Table 4.47 and Figure 4.27. Maximal FN400 amplitude for the interaction occurred at the right posterior electrode elicited by correct recognitions of old words.

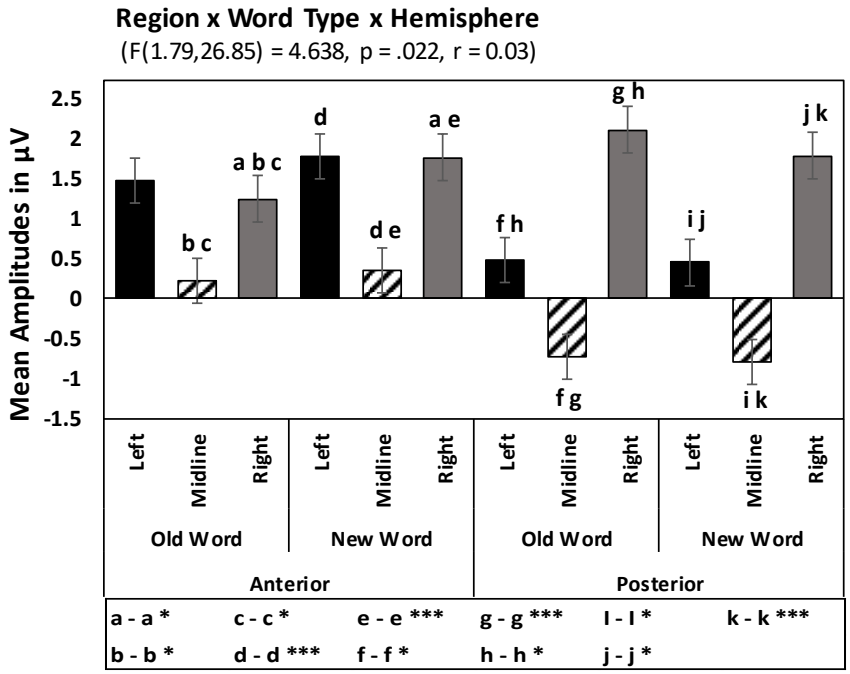
Table 4.46 Word Recognition Old/New FN400 component. Amplitude means and SEMs depicting the region x word type x hemisphere interaction.

Region	Word Type	Hemisphere	Mean	±	SEM
Anterior	Old Word	Left	1.487	±	0.517
		Midline	0.225	±	0.648
		Right	1.256	±	0.489
	New Word	Left	1.786	±	0.312
		Midline	0.355	±	0.331
		Right	1.773	±	0.283
Posterior	Old Word	Left	0.487	±	0.574
		Midline	-0.732	±	0.587
		Right	2.123	±	0.733
	New Word	Left	0.459	±	0.549
		Midline	-0.789	±	0.546
		Right	1.794	±	0.622

Table 4.47 Word Recognition Old/New FN400 component. Significant pairwise comparisons from the Region x Word Type x Hemisphere interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition / Group	Pairwise Differences	Mean(SEM)	t(15)=	p Value
Anterior Region, Right Hemisphere	New Words > Old Words	Old Words (Mean 1.256, SEM 0.489)	2.145	0.049
		New Words (Mean -1.773, SEM 0.283)		
Anterior Region, Old Words	Left > Midline	Left (Mean 1.487, SEM 0.517)	3.626	0.007
		Midline (Mean 0.255, SEM 0.648)		
Anterior Region, Old Words	Right > Midline	Right (Mean 1.256, SEM 0.489)	3.115	0.021
		Midline (Mean 0.255, SEM 0.648)		
Anterior Region, New Words	Left > Midline	Left (Mean 1.786, SEM 0.312)	10.295	<0.001
		Midline (Mean 0.355, SEM 0.331)		
Anterior Region, New Words	Right > Midline	Right (Mean 1.773, SEM 0.283)	8.103	<0.001
		Midline (Mean 0.355, SEM 0.331)		
Posterior Region, Old Words	Left > Midline	Left (Mean 0.487, SEM 0.574)	3.040	0.025
		Midline (Mean -0.732, SEM 0.587)		
Posterior Region, Old Words	Right > Midline	Right (Mean 2.123, SEM 0.733)	6.328	<0.001
		Midline (Mean -0.732, SEM 0.587)		
Posterior Region, Old Words	Right > Left	Right (Mean 2.123, SEM 0.733)	3.252	0.016
		Left (Mean 0.487, SEM 0.574)		
Posterior Region, New Words	Left > Midline	Left (Mean 0.459, SEM 0.549)	3.770	0.006
		Midline (Mean -0.789, SEM 0.546)		
Posterior Region, New Words	Right > Left	Right (Mean 1.794, SEM 0.622)	2.915	0.032
		Left (Mean 0.459, SEM 0.549)		
Posterior Region, New Words	Right > Midline	Right (Mean 1.794, SEM 0.622)	5.870	<0.001
		Midline (Mean -0.789, SEM 0.546)		

Figure 4.27 Word Recognition Old/New FN400 component. pairwise comparison from the region x word type x hemisphere interaction. Figure key shows pairwise comparisons and significance levels. (*p<.05,*p<.001). Bars show standard error.**



There was also a three-way region x valence x word type interaction (F(1.83, 27.43) = 3.441, p = .05, r = 0.08) (see Table 4.45 above and Table 4.48 below for interaction means and SEMs). Significant pairwise comparisons can be found below in Table 4.49 and Figure 4.28. Interaction effects of valence occurred in the anterior region only, with both neutral and positive old words eliciting higher FN400 amplitudes in comparison to negative old words. The effect of word type was also limited to the anterior region with negative new words eliciting higher FN400 amplitudes relative to old words; conversely for neutral words, there was an enhanced FN400 for old words relative to new words. There were no regional effects on the interaction. The FN400 amplitude was maximal in the anterior region evoked by correct recognitions of positive words.

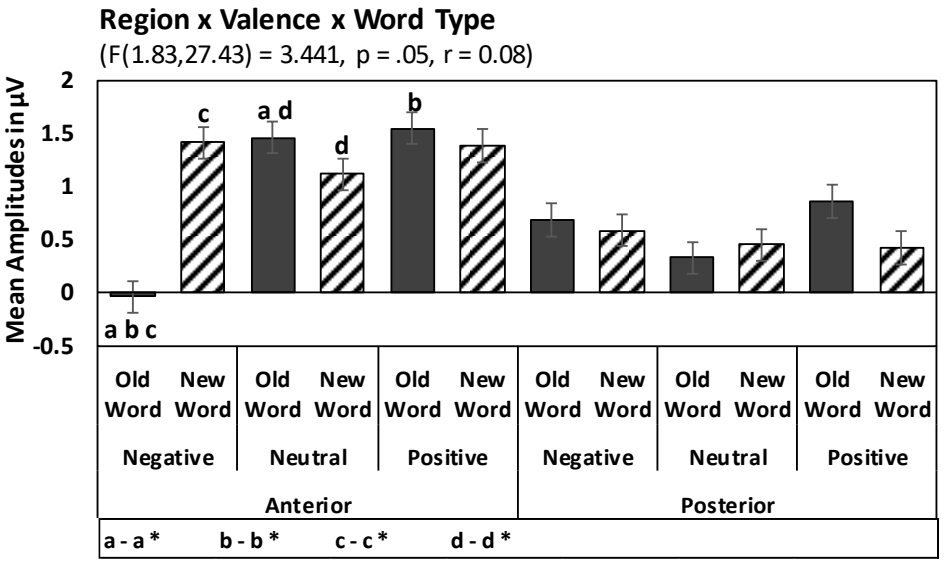
Table 4.48 Word Recognition Old/New FN400 component. Amplitude means and SEMs depicting the region x valence x word type interaction.

Region	Valence	Word Type	Mean	±	SEM
Anterior	Negative	Old Word	-0.041	±	0.831
		New Word	1.414	±	0.268
	Neutral	Old Word	1.462	±	0.37
		New Word	1.116	±	0.309
	Positive	Old Word	1.547	±	0.402
		New Word	1.384	±	0.325
Posterior	Negative	Old Word	0.687	±	0.571
		New Word	0.587	±	0.535
	Neutral	Old Word	0.33	±	0.626
		New Word	0.453	±	0.516
	Positive	Old Word	0.861	±	0.611
		New Word	0.424	±	0.603

Table 4.49 Word Recognition Old/New FN400 component. Significant pairwise comparisons from the Region x Valence x Word Type interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition / Group	Pairwise Differences	Mean(SEM)	t(15)=	p Value
Anterior Region, Old Words	Neutral Words > Negative Words	Neutral Words (Mean 1.462, SEM 0.370)	2.959	0.029
		Negative Words (Mean -0.041, SEM 0.831)		
Anterior Region, Old Words	Positive Words > Negative Words	Positive Words (Mean 1.547, SEM 0.402)	3.208	0.018
		Negative Words (Mean -0.041, SEM 0.831)		
Anterior Region, Negative Words	New Words > Old Words	Old Words (Mean -0.041, SEM 0.831)	2.377	0.031
		New Words (Mean 1.414, SEM 0.268)		
Anterior Region, Neutral Words	Old Words > New Words	Old Words (Mean 1.462, SEM 0.370)	2.291	0.036
		New Words (Mean 1.116, SEM 0.309)		

Figure 4.28 Word Recognition Old/New FN400 component. Pairwise comparison from the region x valence x word type interaction. Figure key shows pairwise comparisons and significance levels. (*p<.05). Bars show standard error.



4.7.2.2 Late positive component (LPC) Old/New Analysis

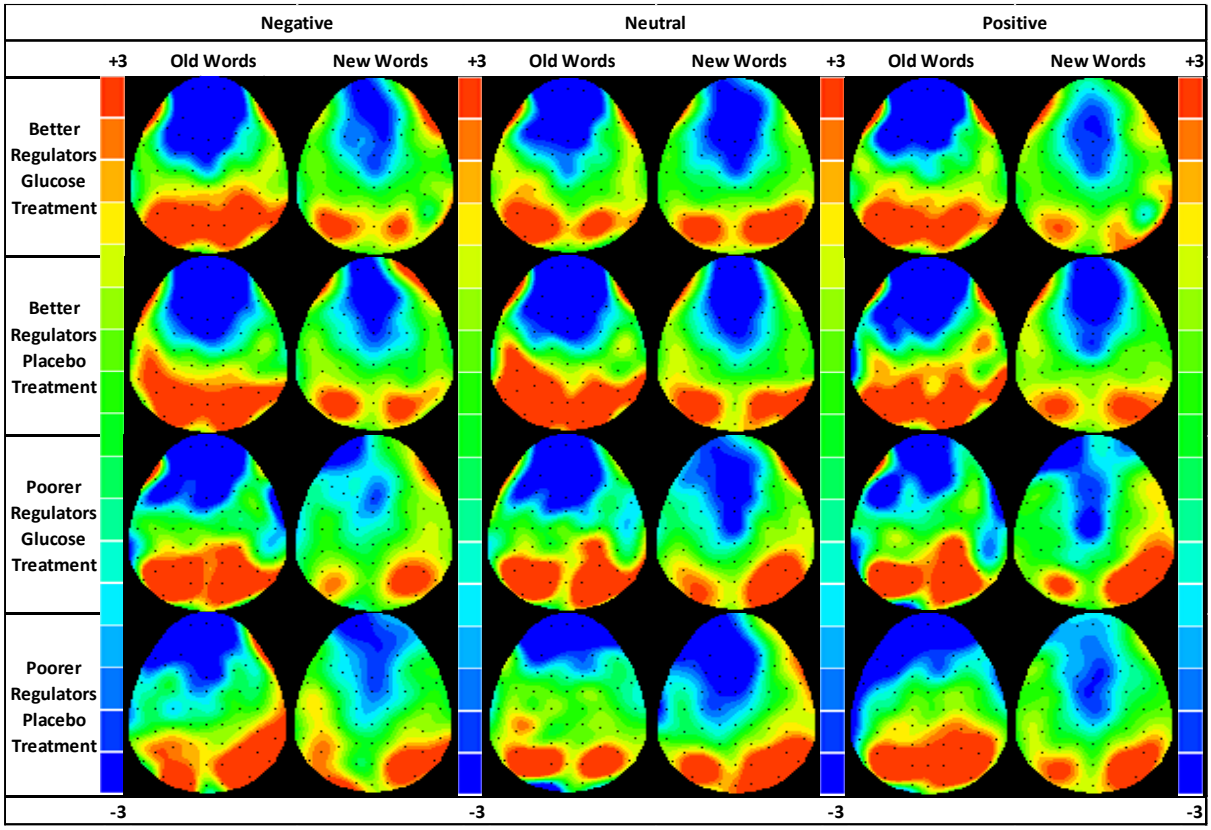
See Appendix 4.8 for the means and SEM for the ERP data for correct recognitions of old words and correct rejections of new words in word recognition phase FN400 component analysis. Significant effects and interactions are indicated.

For the analysis of late positive component data in the 400 – 800ms time window, the primary six-way glucoregulation x treatment x word type x valence x region x hemisphere interaction was non-significant (F(3.41,54.49) = 1.851, p = .142, r = 0.01). Significant main effects and interactions are shown below in Table 4.50. Only significant higher order interactions are reported in the text. Topographical maps representing the LPC component can be seen in Fig. Figure 4.3 below.

Table 4.50 Word Recognition Old/New LPC component. Significant main effects and interactions from the six-way glucoregulation x treatment x word type x valence x region x hemisphere mixed factorial ANOVA conducted on recognition data in the 400 - 800 ms time window. ANOVA F values, degrees of freedom, significance levels and effect sizes are shown.

Main Effect/ Interaction	df	F	p value	r
Valence x Word Type x Hemisphere	(3.02, 48.34)	3.028	0.038	0.03
Region x Word Type	(1,16)	6.595	0.021	0.14
Region	(1,16)	10.643	0.005	0.5
Hemisphere	(1.77,28.24)	18.766	<0.001	0.16

Figure 4.29 Word Recognition Old/New LPC component. ERP topographies of grand average data across the 400-800 ms time window. The colour scale shows amplitude ranges from positive (red) to negative (blue) inflections from +3 to -3 microvolts.



There was a three-way valence x word type x hemisphere interaction (F(3.02, 48.34) = 3.028, p = .038, r = 0.03) (see Table 4.50 above and Table 4.51 below for interaction means and SEMs). Significant pairwise comparisons can be found below in Table 4.52 and Figure 4.30. Valence effects of the interaction showed that the right hemisphere LPC amplitude response to old words was greater for positive words compared to neutral words. Interaction effects of word type revealed enhanced right hemisphere LPC amplitudes elicited by old positive words relative to new positive words. Hemisphere effects show greater LPC amplitudes at the right hemisphere for both old and new words of all valences with the maximal LPC being evoked by correct recognitions of positive old words at the right hemisphere electrodes.

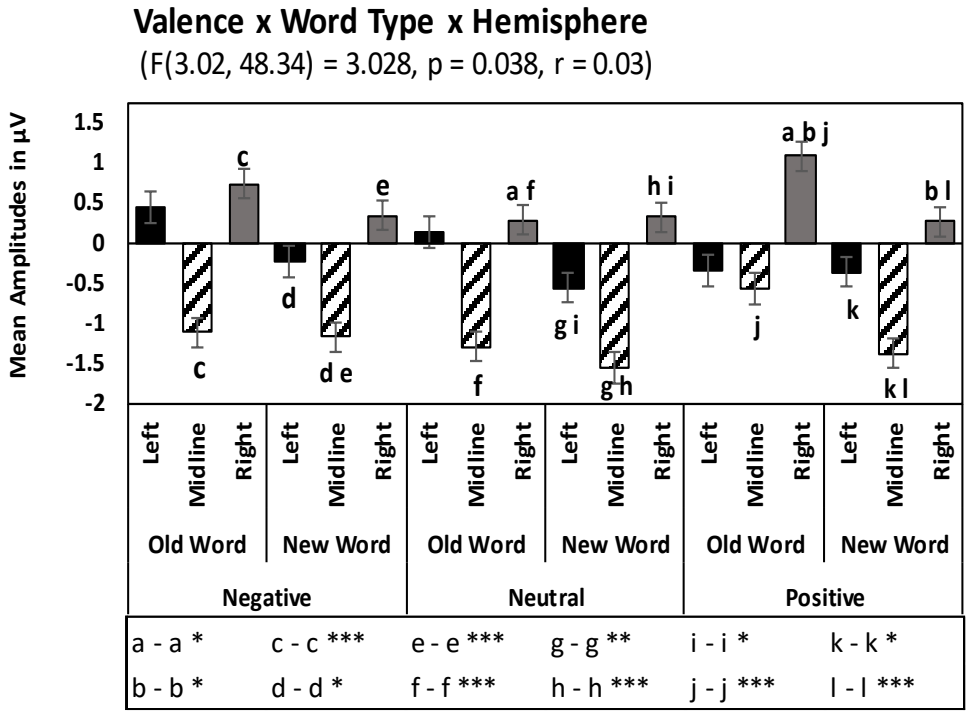
Table 4.51 Word Recognition Old/New LPC component. Amplitude means and SEMs depicting the valence x word type x hemisphere interaction.

Valence	Word Type	Hemisphere	Mean	±	SEM
Negative	Old Word	Left	0.444	±	0.373
		Midline	-1.113	±	0.371
		Right	0.735	±	0.347
	New Word	Left	-0.232	±	0.24
		Midline	-1.167	±	0.291
		Right	0.344	±	0.22
Neutral	Old Word	Left	0.133	±	0.459
		Midline	-1.301	±	0.399
		Right	0.277	±	0.261
	New Word	Left	-0.568	±	0.226
		Midline	-1.559	±	0.249
		Right	0.324	±	0.227
Positive	Old Word	Left	-0.345	±	0.619
		Midline	-0.573	±	0.402
		Right	1.084	±	0.292
	New Word	Left	-0.363	±	0.301
		Midline	-1.387	±	0.338
		Right	0.272	±	0.218

Table 4.52 Word Recognition Old/New LPC component. Significant pairwise comparisons from the Valence x Word Type x Hemisphere interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition / Group	Pairwise Differences	Mean(SEM)	t(15)=	p Value
Old Words, Right Hemisphere	Positive Words > Neutral Words	Positive Words (Mean 1.084, SEM 0.292)	3.335	0.013
		Neutral Words (Mean 0.277, SEM 0.283)		
Positive Words, Right Hemisphere	Old Words > New Words	Old Words (Mean 1.084, SEM 0.292)	2.377	0.030
		New Words (Mean 0.272, SEM 0.218)		
Old Words, Negative Words	Right > Midline	Right (Mean 0.735, SEM 0.347)	5.961	<0.001
		Midline (Mean -1.113, SEM 0.371)		
New Words, Negative Words	Left > Midline	Left (Mean -0.232, SEM 0.240)	3.296	0.014
		Midline (Mean -1.167, SEM 0.291)		
New Words, Negative Words	Right > Midline	Right (Mean 0.344, SEM 0.220)	4.941	<0.001
		Midline (Mean -1.167, SEM 0.291)		
Old Words, Neutral Words	Right > Midline	Right (Mean 0.277, SEM 0.261)	4.885	<0.001
		Midline (Mean -1.301, SEM 0.399)		
New Words, Neutral Words	Left > Midline	Left (Mean -0.568, SEM 0.226)	3.871	0.004
		Midline (Mean -1.559, SEM 0.249)		
New Words, Neutral Words	Right > Midline	Right (Mean 0.324, SEM 0.277)	8.673	<0.001
		Midline (Mean -1.559, SEM 0.249)		
New Words, Neutral Words	Right > Left	Right (Mean 0.324, SEM 0.277)	3.065	0.022
		Left (Mean -0.568, SEM 0.226)		
Old Words, Positive Words	Right > Midline	Right (Mean 1.084, SEM 0.292)	5.021	<0.001
		Midline (Mean -0.573, SEM 0.402)		
New Words, Positive Words	Left > Midline	Left (Mean -0.363, SEM 0.301)	3.531	0.008
		Midline (Mean -1.387, SEM 0.338)		
New Words, Positive Words	Right > Midline	Right (Mean 0.272, SEM 0.218)	5.818	<0.001
		Midline (Mean -1.387, SEM 0.338)		

Figure 4.30 Word Recognition Old/New LPC component. Pairwise comparison from the valence x word type x hemisphere interaction. Figure key shows pairwise comparisons and significance levels. (*p<.05,p<.005,***p<.001). Bars show standard error.**



The two-way region x word type interaction was found to be significant (F(1,16) = 6.595, p = .021, r = 0.14), (see Table 4.50 above and Table 4.51 below for interaction means and SEMs). Significant pairwise comparisons can be found below in Table 4.54 and Figure 4.31. Both old and new words elicited higher posterior LPC amplitudes with the posterior LPC being greater for old words compared to new words. Interaction maximal LPC amplitude was seen at the posterior region elicited by correct recognitions of old words.

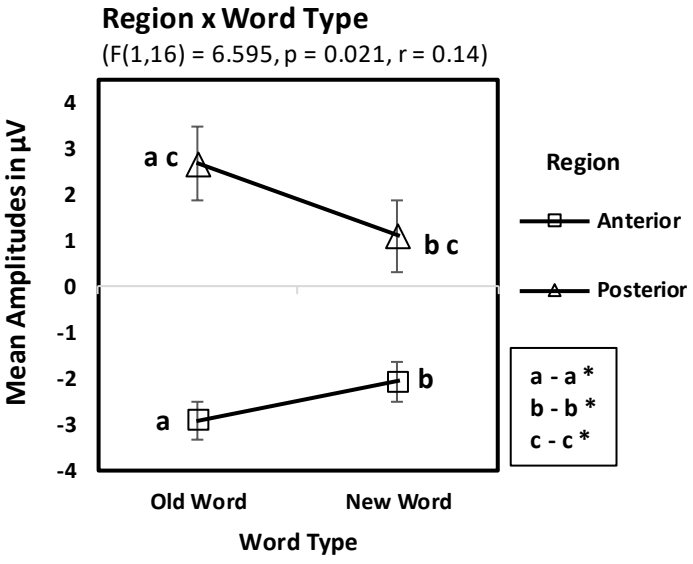
Table 4.53 Word Recognition Old/New LPC component. Amplitude means and SEMs depicting the region x word type interaction.

Region	Word Type	Mean	±	SEM
Anterior	Old Word	-2.918	±	1.059
	New Word	-2.069	±	0.62
Posterior	Old Word	2.683	±	0.735
	New Word	1.106	±	0.439

Table 4.54 Word Recognition Old/New LPC component. Significant pairwise comparisons from the Region x Word Type interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition / Group	Pairwise Differences	Mean(SEM)	t(16)=	p Value
Old Words	Posterior > Anterior	Posterior (Mean 2.683, SEM 0.735)	3.213	0.005
		Anterior (Mean -2.918, SEM 1.059)		
New Words	Posterior > Anterior	Posterior (Mean 1.106, SEM 0.439)	3.134	0.006
		Anterior (Mean --2.069, SEM 0.439)		
Posterior Region	Old Words > New Words	Old Words (Mean 2.683, SEM 0.735)	3.225	0.005
		New Words (Mean -1.106, SEM 0.439)		

Figure 4.31 Word Recognition Old/New LPC component. Pairwise comparison from the region x word type interaction. Figure key shows pairwise comparisons and significance levels. (*p<.05). Bars show standard error.



4.7.2.2.1 Summary of Word Recognition Old/New ERP Data Results

In the 300 - 500 ms time window, analysis of the FN400 component data for old and new recognitions identified an interaction between region, word type and hemisphere. Interaction effects of word type found greater right anterior FN400 amplitudes for new words relative to old words. The interaction between region, valence and word type identified effects of valence and word type both of which were limited to the anterior region. Neutral and positive old words evoked greater anterior FN400 amplitudes compared to old negative words. Negative new words elicited higher anterior amplitudes relative to negative old words but for neutral words this was reversed with greater amplitudes for old compared to new words. There were no significant regional differences in FN400 amplitudes for either of these interactions.

In the 400 - 800 ms time window, analysis of the LPC component data for old and new recognitions identified an interaction between valence, word type and hemisphere. Positive old words elicited greater LPC right hemisphere amplitudes than did old neutral words. In terms of word type, right hemisphere LPC amplitudes were greater for correct recognitions of positive old words compared to correct rejections of positive new words. All words elicited greater LPC amplitudes in the right hemisphere with amplitudes being maximal for correct recognitions of old positive words. The region x word type interaction showed enhanced posterior LPC amplitudes for both old and new words with greater amplitudes for correctly recognised old words than for correctly rejected new words.

4.7.3 Remember / Know

For correct recognition responses to old words participants subjective 'remember' or 'know' judgements were assessed. With a view to making comparisons between both ERP and behavioural old/new analysis participants subjective measures of recollection and familiarity were also analysed for the FN400 component 300 – 500ms and the LPC component 400 – 800ms time windows.

4.7.3.1 FN400 positive going component.

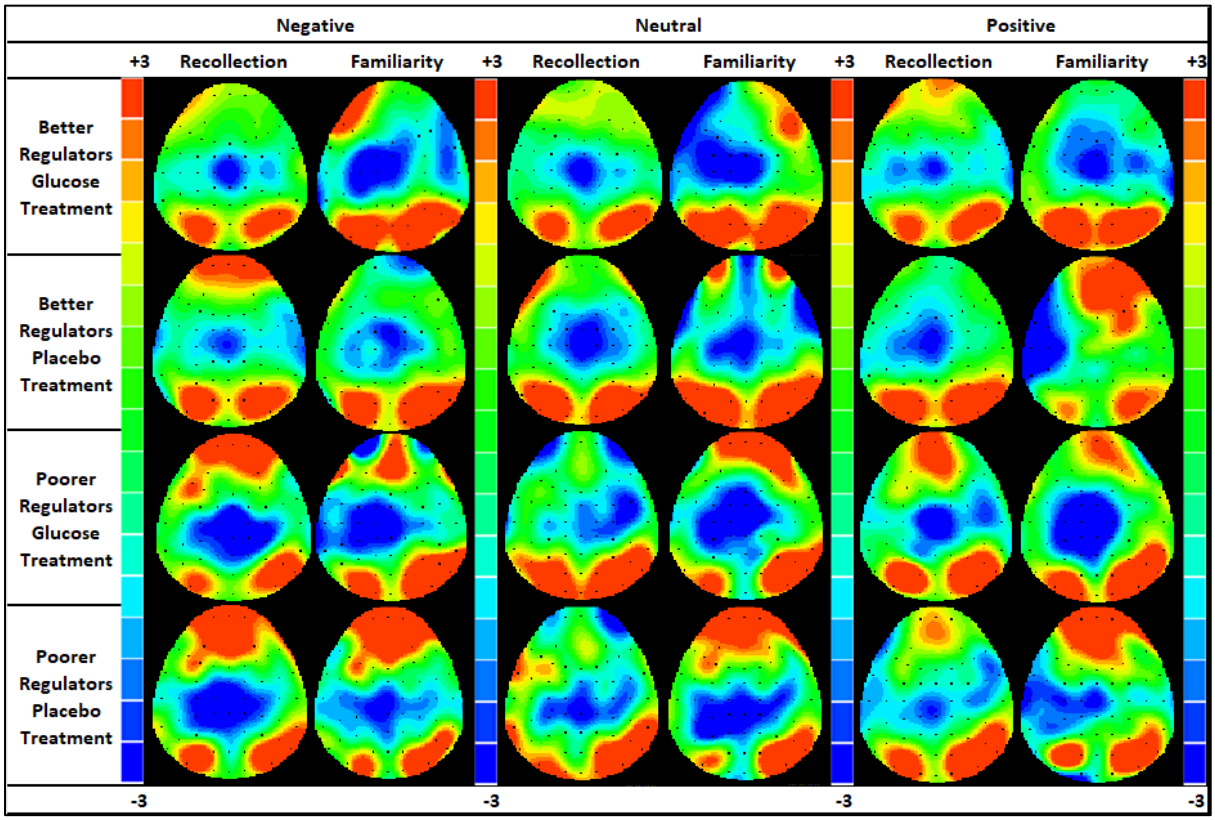
See Appendix 4.8 for the means and SEM for the ERP data for the subjective judgements of correctly recognised old words in word recognition phase FN400 component analysis. Significant effects and interactions are indicated.

The primary six-way glucoregulation x treatment x region x valence x recognition type x hemisphere interaction was non-significant (F(2.93,38.04) = 0.734, p = .535). Significant main effect and interaction are shown below in Table 4.55. Topographical maps representing the FN400 component can be seen in Figure 4.32 below.

Table 4.55 Word Recognition Remember/Know FN400 component. Significant main effects and interactions from the six-way glucoregulation x treatment x recognition type x valence x region x hemisphere mixed factorial ANOVA conducted word recognition phase data in the 300 - 500 ms time window. ANOVA F values, degrees of freedom, significance levels and effect sizes are shown.

Main Effect/ Interaction	df	F	p value	r
Glucoregulation x treatment x recognition type x valence	(1.73,22.44)	4.11	.035	0.07
Hemisphere	(1.96,25.42)	6.491	.006	0.13

Figure 4.32 Word Recognition Remember/Know FN400 component. ERP topographies of grand average recognition type data for FN400 component across the 300-500 ms time window. The colour scale shows amplitude ranges from positive (red) to negative (blue) inflections from +3 to -3 microvolts.



There was a significant four-way glucoregulation x treatment x recognition type x valence interaction ($F(1.73,22.44) = 4.11$, $p = .035$, $r = 0.07$) (see Table 4.55 above and Table 4.56 below for interaction means and SEMs), significant pairwise comparisons can be found below in Table 4.57 and Figure 4.33. Glucoregulation effects on the interaction showed that poorer regulators, responding to negative words elicited greater FN400 amplitudes for 'familiarity' judgements compared to better regulators. Interaction effects of treatment showed for poorer regulators, FN400 amplitude responses to familiarity judgements of negative words were greater following glucose, relative to placebo. Valence effects revealed that following glucose familiarity judgements of negative words elicited greater amplitudes compared to familiarity judgements of both neutral and positive words. Interaction effects of recognition type showed that following glucose better regulators elicited greater amplitude responses for recollection judgements of neutral words compared to familiarity judgements of neutral words.

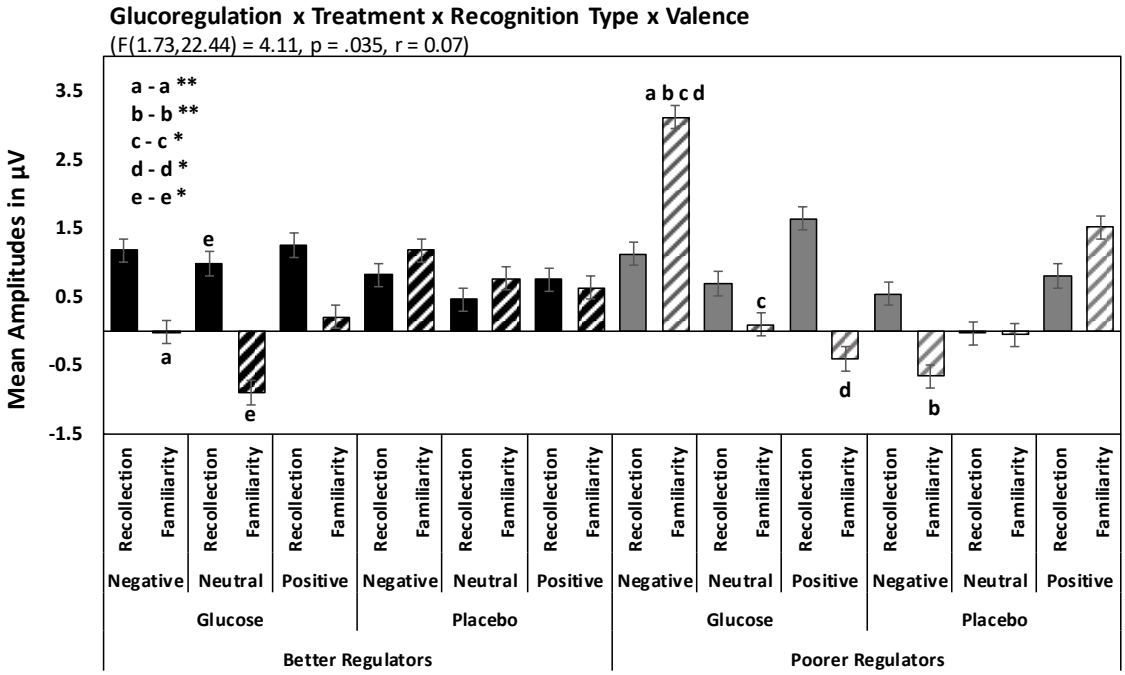
Table 4.56 Word Recognition Remember/Know FN400 component. Amplitude means and SEMs depicting the glucoregulation x treatment x recognition type x valence interaction.

Glucoregulation	Treatment	Emotion	Recognition Type	Mean	±	SEM
Better Regulators	Glucose	Negative	Recollection	1.175	±	0.624
			Familiarity	-0.015	±	0.446
		Neutral	Recollection	0.98	±	0.501
			Familiarity	-0.907	±	0.548
		Positive	Recollection	1.249	±	0.455
			Familiarity	0.204	±	0.791
	Placebo	Negative	Recollection	0.818	±	0.487
			Familiarity	1.175	±	0.778
		Neutral	Recollection	0.458	±	0.613
			Familiarity	0.763	±	0.795
		Positive	Recollection	0.747	±	0.437
			Familiarity	0.63	±	0.715
Poorer Regulators	Glucose	Negative	Recollection	1.123	±	0.882
			Familiarity	3.121	±	0.63
		Neutral	Recollection	0.686	±	0.708
			Familiarity	0.092	±	0.775
		Positive	Recollection	1.636	±	0.644
			Familiarity	-0.412	±	1.118
	Placebo	Negative	Recollection	0.54	±	0.688
			Familiarity	-0.669	±	1.1
		Neutral	Recollection	-0.039	±	0.867
			Familiarity	-0.058	±	1.124
		Positive	Recollection	0.804	±	0.618
			Familiarity	1.514	±	1.011

Table 4.57 Word Recognition Remember/Know FN400 component. Significant pairwise comparisons from the glucoregulation x treatment x recognition type x valence interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

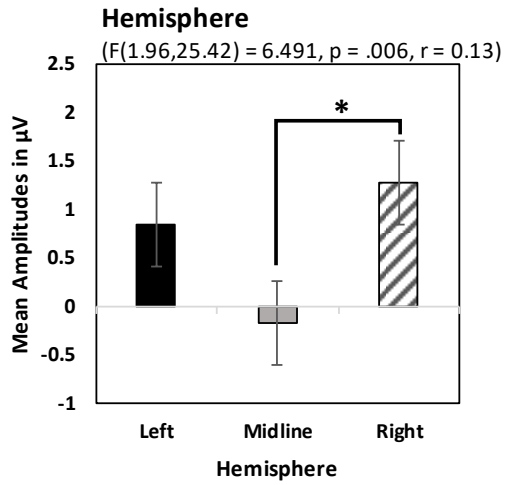
Condition / Group	Pairwise Differences	Mean(SEM)	t(15)=	p Value
Glucose, Negative Words, Familiarity	Poorer > Better Regulators	Poorer (Mean 3.121, SEM 0.630)	4.061	0.001
		Better (Mean -0.015, SEM 0.446)		
Poorer Regulators, Negative Words, Familiarity	Glucose > Placebo	Glucose (Mean 3.121, SEM 0.630)	3.655	0.003
		Placebo (Mean -0.669, SEM 1.1100)		
Poorer Regulators, Glucose, Familiarity	Negative > Neutral Words	Negative (Mean 3.121, SEM 0.630)	2.878	0.039
		Neutral (Mean -0.092, SEM 0.775)		
Poorer Regulators, Glucose, Familiarity	Negative > Positive Words	Negative (Mean 3.121, SEM 0.630)	2.869	0.040
		Positive (Mean -0.412, SEM 1.118)		
Better Regulators, Glucose, Neutral Words	Recollection > Familiarity	Recollection (Mean 0.980, SEM 0.501)	2.855	0.013
		Familiarity (Mean -0.907, SEM 0.548)		

Figure 4.33 Word Recognition Remember/Know FN400 component. Pairwise comparisons from the glucoregulation x treatment x recognition type x valence interaction. Figure key shows pairwise comparisons and significance levels. (*p<.05,p<.005). Bars show standard error.**



There was also a main effect of hemisphere (F(1.96,25.42) = 6.491, p = .006, r = 0.13) (see Table 4.55 above) showing that FN400 component mean amplitude was greater at right hemisphere electrodes (Mean 1.278, SEM 0.304) relative to midline electrodes (Mean -0.174, SEM 0.431) (t(16) = 3.801, p = .007). Amplitudes were maximal at the right hemisphere, see Figure 4.34.

Figure 4.34 Word Recognition Remember/Know FN400 component. Pairwise comparisons from the main effect of hemisphere. See figure key for significance levels (*p<.05). Bars show standard error.



4.7.3.2 Late positive (LP) positive going component.

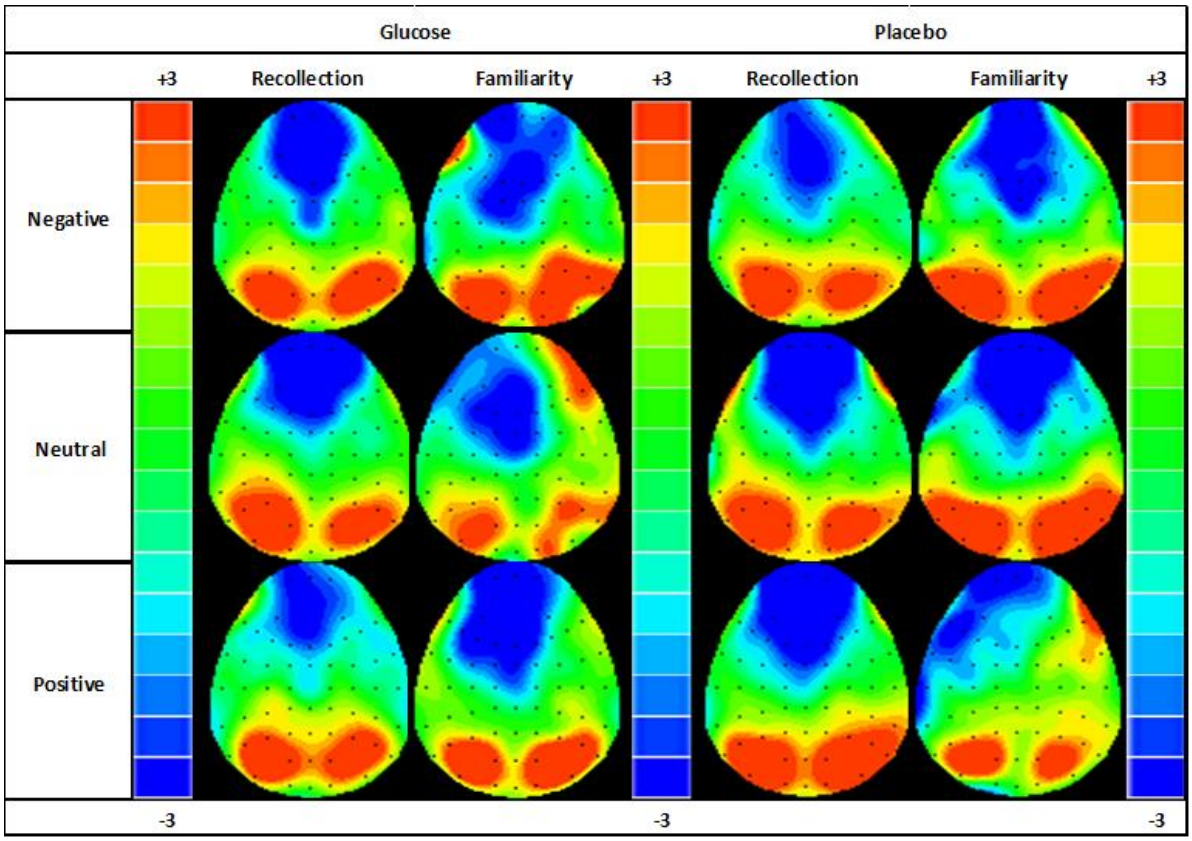
See Appendix 4.10 for the means and SEM for the ERP data for the subjective judgements of correctly recognised old words in word recognition phase LPC component analysis. Significant effects and interactions are indicated.

The primary six-way glucoregulation x treatment x region x valence x recognition type x hemisphere interaction was non-significant (F(2.67,34.74) = 0.627, p = .585, r = 0.02). Significant main effects and interactions are shown below in Table 4.58. Topographical maps representing the LPC component can be seen in Figure 4.35 below.

Table 4.58 Word Recognition Remember/Know LPC component. Significant main effects and interactions from the six-way glucoregulation x treatment x recognition type x valence x region x hemisphere mixed factorial ANOVA conducted word recognition phase data in the 400 - 500 ms time window. ANOVA F values, degrees of freedom, significance levels and effect sizes are shown.

Main Effect/ Interaction	df	F	p value	r
Treatment x valence x recognition type	(1.78,23.16)	5.323	.015	0.05
Glucoregulation x recognition type	(1,13)	4.750	.048	0.03
Treatment x recognition type	(1,13)	8.109	.014	0.05
Recognition type	(1,13)	6.286	.021	0.04
Region	(1,13)	11.552	.005	0.50
Hemisphere	(1,13)	19.008	<.001	0.16

Figure 4.35 Word Recognition Remember/Know LPC component. ERP topographies of grand average data for LPC component across the 400-800 ms time window. The colour scale shows amplitude ranges from positive (red) to negative (blue) inflections from +3 to -3 microvolts.



The three-way treatment x valence x recognition type interaction ($F(1.78,23.16) = 5.323$, $p = .015$, $r = 0.5$) (see Table 4.58 above, and Table 4.59 below for interaction means and SEMs. Significant pairwise comparisons can be found below in **Table 4.60** and **Figure 4.36**). Glucose enhanced LPC amplitudes for the recollection of positive words relative to placebo; this was reversed for familiarity where the LPC amplitude was higher following placebo. Positive words elicited higher familiarity LPC amplitudes than negative words following placebo. Recognition type effect on the interaction showed that for recollection judgements LPC evoked by positive words was greater than for familiarity judgements of positive words.

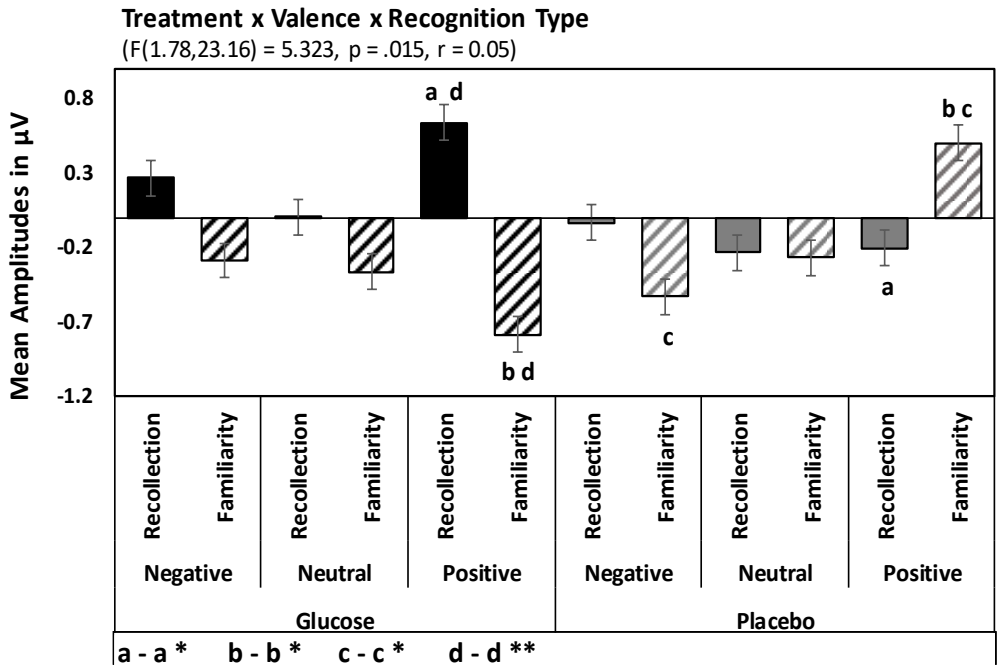
Table 4.59 Word Recognition Remember/Know LPC component. Amplitude means and SEMs depicting the treatment x valence x recognition type interaction.

Treatment	Emotion	Recognition Type	Mean	±	SEM
Glucose	Negative	Recollection	0.269	±	0.295
		Familiarity	-0.289	±	0.358
	Neutral	Recollection	0.004	±	0.401
		Familiarity	-0.368	±	0.484
	Positive	Recollection	0.641	±	0.299
		Familiarity	-0.786	±	0.395
Placebo	Negative	Recollection	-0.037	±	0.29
		Familiarity	-0.531	±	0.504
	Neutral	Recollection	-0.234	±	0.422
		Familiarity	-0.27	±	0.302
	Positive	Recollection	-0.204	±	0.34
		Familiarity	0.501	±	0.543

Table 4.60 Word Recognition Remember/Know LPC component. Significant pairwise comparisons from the treatment x valence x recognition type interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition / Group	Pairwise Differences	Mean(SEM)	t(15)=	p Value
Positive Words, Recollection	Glucose > Placebo	Glucose (Mean 0.641, SEM 0.299)	2.914	0.012
		Placebo (Mean -0.204, SEM 0.340)		
Positive Words, Familiarity	Placebo > Glucose	Placebo (Mean 0.501, SEM 0.543)	2.854	0.014
		Glucose (Mean -0.669, SEM 1.1100)		
Placebo, Familiarity	Positive > Negative Words	Positive (Mean 0.501, SEM 0.543)	2.782	0.039
		Negative (Mean -0.531, SEM 0.504)		
Glucose, Positive Words	Recollection > Familiarity	Recollection (Mean 0.641, SEM 0.299)	4.020	0.001
		Familiarity (Mean -0.786, SEM 0.395)		

Figure 4.36 Word Recognition Remember/Know LPC component. Pairwise comparisons from the treatment x valence x recognition type interaction. Figure key shows pairwise comparisons and significance levels. (*p<.05,p<.005). Bars show standard error.**

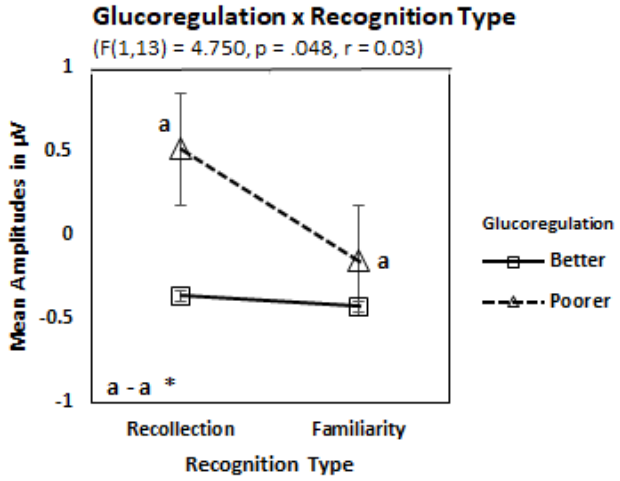


The two-way glucoregulation x recognition type interaction (F(1,13) = 4.11750, p = .048, r = 0.03) (see Table 4.58 above and Table 4.61 below for interaction means and SEMs). Pairwise comparisons revealed that interaction recognition type effects showed poorer glucoregulators eliciting greater LPC component amplitudes for 'recollection' judgements than they did for 'familiarity' judgements, (t(16) = 2.938, p = .012). There were no effects of glucoregulation on the interaction. See Figure 4.37 below.

Table 4.61 Word Recognition Remember/Know LPC component. Amplitude means and SEMs depicting the glucoregulation x recognition type interaction.

Glucoregulation	Recognition Type	Mean	±	SEM
Better Regulators	Recollection	-0.366	±	0.317
	Familiarity	-0.427	±	0.381
Poorer Regulators	Recollection	0.512	±	0.449
	Familiarity	-0.154	±	0.539

Figure 4.37 Word Recognition Remember/Know LPC component. Pairwise comparisons from the glucoregulation x recognition type interaction. Figure key shows pairwise comparisons and significance levels. (*p<.05). Bars show standard error.

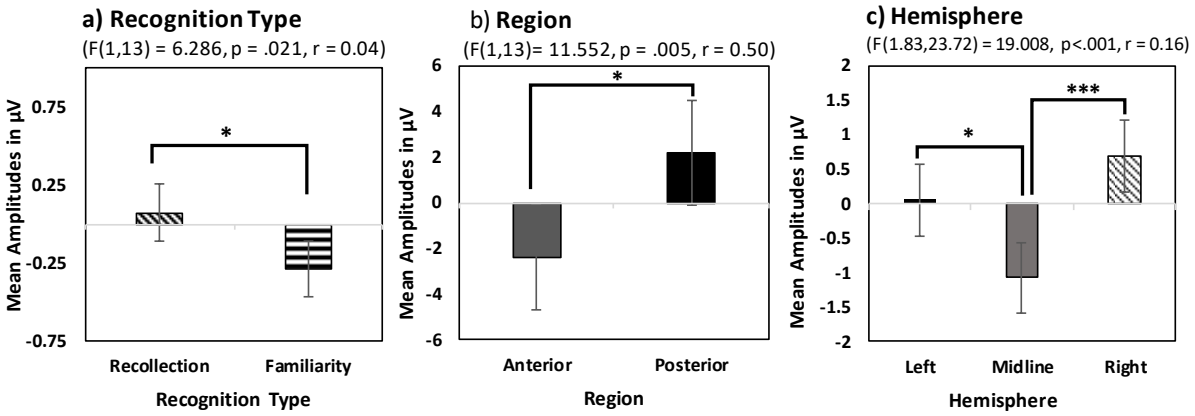


The main effect of recognition type (F(1,13) = 6.286, p = .021, r = 0.04) (see Table 4.58 above) showed 'recollection' judgements (MEAN 0.073, SEM 0.275) elicited greater LP component amplitudes than did 'familiarity' judgements (Mean -0.291, SEM 0.330).See Figure 4.38(a).

There was a main effect of region (F(1,13) = 11.552, p = .005, r = 0.50) (see Table 4.58 above) which revealed that the LP component amplitude was greater at the posterior region (Mean 2.172, SEM 0.598) relative to the anterior region (Mean -2.390, SEM 0.847). See Figure 4.38(b).

The main effect of hemisphere (F(1,13) = 19.008, p<.001, r = 0.16) (see Table 4.58 above) revealed that compared to midline electrode sites (Mean -1.073, SEM 0.396) left hemisphere electrodes were greater (Mean 0.053, SEM 0.330) (t(16)= 3.443, p = .013). Also relative to midline electrodes, right hemisphere sites (Mean 0.693, SEM 0.283) were greater (t(16) = 7.125, p<.00005). LP component amplitude was maximal at the right hemisphere electrodes. See Figure 4.38(c).

Figure 4.38 Word Recognition Remember/Know LPC component. Pairwise comparisons from the main effects of recognition type, region, and hemisphere. Figure key shows pairwise comparisons and significance levels. (*p<.05,*p>.001). Bars show standard error.**



4.7.3.2.1 Summary of Word Recognition Remember/Know ERP Data Results

In the 300 - 500 ms time window, analysis of the FN400 component data for the subjective judgements of correctly recognised old words identified an interaction between glucoregulation, treatment, recognition type and valence. Poorer regulators familiarity responses to negative words evoked a higher FN400 than did better regulators and in poorer regulators only this effect was enhanced by glucose ingestion. Again, for poorer regulators, following glucose familiarity responses to negative words elicited greater FN400 amplitudes compared to both neutral and positive words. Additionally, following glucose and for neutral word judgements, better regulators were observed to have greater FN400 amplitudes when making recollection judgements relative to familiarity judgements.

In the 400 - 800 ms time window, analysis of the LPC data for the subjective judgements of correctly recognised old words identified an interaction between treatment, valence and recognition type which showed recollection judgements of positive words eliciting a greater LPC following glucose and this effect was reversed for familiarity judgements where following placebo positive words had greater LPC amplitudes. In terms of valence effects, familiarity judgements of positive words evoked greater LPC amplitudes than did negative words. Additionally, following glucose recollection judgements elicited higher amplitudes than familiarity judgements of positive words.

The interaction between glucoregulation and recognition type identified that whilst there were no glucoregulation effects, poorer regulators evoked greater LPC amplitudes for recollection judgements compared to familiarity judgements.

Main effects of recognition type, region and hemisphere revealed respectively that LPC amplitudes were greater for recollection judgements than familiarity judgements, amplitudes were higher in the posterior than the anterior region and the left and right hemisphere LPCs were greater than at midline electrodes with a maximal LPC seen at the right hemisphere electrodes.

4.8 Discussion

4.8.1 Summary of Main Findings

The principle aim of this chapter was to explore the potential effect of glucoregulatory control and circulatory blood glucose levels on episodic memory for neutral and emotionally valenced words. Evaluation of glucoregulatory control was facilitated by a median split based on participants evoked blood glucose levels. Both behavioural and neurophysiological measures, specifically ERP correlates of episodic memory, were utilised to investigate the impact of glucoregulation and ingested glucose on the accuracy of episodic memory. Additionally, to investigate whether glucoregulation or glucose ingestion mediated memory type, participants' subjective assessment of the memory strength of correct recognitions of old words was assessed via the recollection and familiarity paradigm. Heart rate was also monitored to explore whether there was mediation of physiological effects of glucoregulation and glucose ingestion in response to the encoding of emotional words.

4.8.1.1 Blood Glucose

Based on the evoked levels of circulating blood glucose, calculated from the OGTT on the practice visit, a median split was used to divide participants into better glucoregulators and poorer glucoregulators. A one-way ANOVA, conducted on better vs. poorer glucoregulators, confirmed that response to the glucose load was highly significant between the two groups and as such demonstrated that the median split was a valid division of the glucoregulator type variable. On test days, as would be expected from a cohort of healthy young adults, baseline blood glucose levels were all within the normal healthy range and did not differ between poorer and better glucoregulators. A highly significant treatment x time interaction confirmed that circulatory blood glucose levels were effectively elevated by the glucose dose during the testing period.

4.8.1.2 Heart Rate

Two research questions were applied here, firstly that glucose ingestion would accelerate heart rate beats per minute overall. The second research question posited that if heart rate was modulated by the emotionality of the stimuli a deceleration of BPM would be seen following placebo and in response to negative word display. Unexpectedly, there were no significant findings for analysis of heart rate data. However, observation of the means revealed that poorer glucoregulators had consistently higher heart rates than better glucoregulators. As all participants were healthy young adults; it may be that heart rate differences were too subtle to be detected in this population.

4.8.1.3 Flanker Task

Research questions for the Flanker task suggested that poorer glucoregulators would have diminished sustained attention performance compared to better regulators. Further, if glucose enhancement is only seen in populations with challenged glucoregulatory control, then glucose ingestion would benefit the performance of poorer regulators. There were, however, no significant effects of glucoregulation or ingested glucose seen in these data. Responses to both congruent and neutral flanker arrays were more accurate than to incongruent or NO/GO arrays and globally slower responses were made to incongruent compared to congruent and neutral flanker arrays. The less accurate performance for NO/GO arrays indicates deficits in sustained attention. However, whilst accuracy was not significantly different for these conflicted arrays it may be that a more stringent task would evoke more errors.

4.8.1.4 Word Recognition Encoding

The ERP study data enabled the neurophysiology of encoding to be explored, which is not available from solely behavioural studies. In terms of encoding, this chapter explored whether ERP component amplitudes would be differentially modulated by 'better' and 'poorer' glucoregulators and/or ingested glucose? There were no effects of glucoregulation, or glucose ingestion observed in the analysis of the P1 and N1 components.

In the 300 – 500 ms time window of the P3 component, glucoregulation effects were seen with better glucoregulators having a greater left anterior P3 relative to poorer regulators following placebo. When glucose ingestion was in play, poorer regulators only had a significantly greater right

posterior P3 than anterior P3. The P3 analysis suggests that glucose is modulating neural activity in poorer, but not better regulators here, which may support the argument that these poorer regulators, who may have impaired ability to restore depleted interstitial brain glucose, may be benefitting from the glucose dose (Convit, 2005; Lamport et al., 2009; Young & Benton, 2014).

The LPC analysis of the 400 – 800 ms time window did not reveal any significant comparisons between the glucoregulation groups. Better regulators, but not poorer regulators, had greater posterior than anterior LPC amplitudes following glucose ingestion. In terms of the glucose dose, this was seen to modulate amplitude responses to positive words with a smaller LPC relative to following placebo.

This ERP investigation of the encoding phase of recognition memory provides evidence that the neurophysiological correlates of memory encoding, indexed by the P3 component in the 300 – 500 ms latency window, are modulated by both glucoregulatory control and ingested glucose. There was also evidence that the LPC component in the 400 – 800 latency window is modulated by glucose ingestion. However, whilst these findings provide some evidence to support the relevant research questions, it was not possible to make neurological associations between encoding effects and subsequent recognition memory outcomes.

4.8.1.5 Word Recognition Old/New

There was no behavioural support for glucoregulatory effects or treatment effects for the recognition of old and new words. Accuracy was greater for correct rejections of new words of all valence types compared to correct recognitions of old words. For correct rejections of new words, accuracy for neutral word responses was greater than for both negatively and positively valenced words. Response speed data identified faster responses to correctly rejected new words relative to correctly recognised old word responses. Replicating the outcome from chapter 3, responses were made more slowly for both negative and positive words compared to neutral words which may be indicative of the slower processing of additional attentional resources involved in the processing of emotionally valenced stimuli.

In terms of the neurological data, in the earlier 300 – 500 ms time window FN400 analysis of recognition accuracy for correctly recognised old or correctly rejected words did not reveal any glucoregulation or treatment effects. Differences in word type were seen with greater right anterior

FN400 amplitudes for new words compared to old words which was contrary to expectations that greater positivity in the FN400 is indicative of memory strength. Greater FN400 amplitudes were seen for responses to both neutral and positive words relative to negative words.

4.8.1.6 Word recognition Remember/Know

Analysis of behavioural data for the subjective measures of memory type, via the Remember/Know paradigm, revealed valence effects with participants' familiarity responses more biased toward negative and positive, as opposed to neutral responses. For inaccurate recognitions there were more recollection errors than familiarity errors. There were no significant treatment, or glucoregulation effects observed in the behavioural data.

ERP analysis of correctly recognised 'old' previously seen words provided the opportunity to explore the effects of ingested glucose on memory strength, as such subjective 'remember' judgements signified items associated with the episodic richness of recollection, and 'know' judgements were indicative of familiarity, unsupported by contextual detail. The research questions related to subjective responses posits that if glucose facilitation is subserved by the demand approach, then both recollection and familiarity would be enhanced by glucose ingestion. On the other hand, if the glucose effect was domain specific and subserved by the hippocampus then only ERP amplitude modulation of recollection would be observed. Traditionally, the FN400 component in this latency window is believed to index familiarity at mid-anterior sites and indeed, glucose was seen to modulate FN400 amplitudes relating to familiarity judgements in this earlier latency window, providing evidence for the more global enhancement attributed to the demand approach. Conventionally, the Late Positive Component (LPC), in the 400 – 800ms time window, is typically believed to index recollection and here, glucose was seen to elevate LPC amplitudes evoked by recollection judgements, lending support to the domain approach.

A further research question addressed here conjectured that if early cognitive decrements are present in the 'poorer' glucoregulatory group and as glucose has been demonstrated to target compromised populations, glucose would have a facilitative effect on 'poorer' but not 'better' regulators. Support for this was evidenced by glucose being seen to facilitate poorer regulators, with FN400 amplitude responses to familiarity judgements of negative words being greater following glucose, relative to placebo. Additionally, poorer regulators, responding to negative words elicited greater FN400 amplitudes for 'familiarity' judgements compared to better regulators.

4.8.2 Limitations

Whilst no effects of glucoregulatory control or ingested glucose were observed in the behavioural word recognition data, they were seen in the much more nuanced neurophysiological data. Previous research has suggested that glucose enhancement is only seen when tasks necessitate a high intensity of cognitive demand (Brandt, Gibson, & Rackie, 2013; Fairclough & Houston, 2004; Kennedy & Scholey, 2000; Riby, 2004; Scholey et al., 2013; Scholey, Harper, & Kennedy, 2001; Scholey, Laing, & Kennedy, 2006; Sünram-Lea, Foster, Durlach, & Perez, 2002). To explore this further, in chapter 5 cognitive demand will be manipulated by the inclusion of a high/low effort secondary task during the encoding phases of the word recognition task.

The Flanker conflict task did not identify any effects of glucoregulation or glucose ingestion, however it may be possible that the screen timeouts were too long to invoke errors. As there was evidence that the Go / NoGo conflict paradigm was effective, chapter 5 will shorten the display timings and increase the ratio of conflict by utilising a more stringent Sustained Attention to Response Task (SART) (Robertson et al., 1997).

Differentially to chapters 2 and 3, which used between-groups designs, no baseline measures of cognitive tasks were taken for chapter 4 which utilised a within-groups design based on treatments, glucose or placebo drinks were administered prior to testing. Comparisons were made across treatment conditions rather than participants performing a baseline assessment at each visit. The rationale for this was that as the sessions already lasted for a minimum of 1.5 hours, considering the lengthy capping process, blood sampling and drink consumption and absorption, adding a further 45 minutes of sitting still to avoid disturbance of EEG and ECG electrodes would have been tiring and uncomfortable for participants. Additionally, and importantly the electrical impedances of the EEG electrodes, which were all kept to a minimum, tend to drift with time and movement, and it was felt that as this would all be reflected in the post-treatment data, comparison between baseline and post-treatment would not have been robust.

The lack of a significant difference in blood glucose levels between glucoregulation groups on test days was unexpected and two possible explanations for this could be argued. Primarily it may be that as all participants glucose tolerance, as defined by the OGTT, was within a normal healthy range, differences between the groups were not significant. Alternatively, this may highlight potential limitations of a median split. The practice of median splits has been has been defended by (Iacobucci

et al., 2007) who suggest that the series of statistical simulations and the advantages of modelling structural equations has found the technique to be robust. Conversely, there is an argument that median splits utilised to create a dichotomous variable based on a median split of a continuously measured variable, can raise incidences of Type 2 errors due to loss of power and increases in Type 1 errors (McClelland et al., 2015).

4.8.3 Conclusion

The main objective of Chapter 4 was to investigate the role of glucose ingestion and early, sub-clinical deficits in glucoregulatory control, in modulating cognitive performance in healthy young non-diabetic adults. This chapter sought to clarify the often contradictory findings reported in the literature and extend existent knowledge through the inclusion of emotional stimuli that draw on a wider range of attentional resources.

Whilst no treatment or glucoregulation effects were seen in the behavioural data, there were faster responses to correct rejections of new words compared to correct recognitions of old words. This speeding of responses to new words may suggest that less extensive processing is required for a correct rejection judgement than for the retrieval process involved in the correct recognition of a previously seen word. Additionally, the faster recognition response speeds for neutral, compared to both negative and positively valenced stimuli, offers credence to the notion that increased attentional resources are required to process emotionally valanced stimuli. This suggests that task demand is in play, with reaction times attenuated by more extensive global processing. Given that there is evidence to suggest that glucose enhancement of verbal memory is only seen in this population of healthy young adults when high cognitive demand is in play (Brandt, Nielsen, & Holmes, 2013; Fairclough & Houston, 2004; Kennedy & Scholey, 2000; Riby, et al., 2004; Scholey, et al., 2001, 2006; Sünram-Lea, et al., 2002); this outcome may tentatively support previous research suggesting that glucose facilitation is mediated by task effort rather than hippocampal involvement (Scholey et al., 2009; 2013). Supporting evidence for this paradigm was also seen in the neurophysiological data, with significant interactions in both the FN400, and LPC experimental time-windows following the same pattern of emotionality; here expressed as greater mean amplitudes for both positive and negative stimuli. Glucoregulation and treatment effects were also present in the ERP effects observed.

Glucoregulation and treatment effects were evident in the more nuanced neurophysiological data, with both glucoregulatory control and glucose administration modulating ERP amplitudes of the FN400 component. FN400 analysis, across the earlier 300-500 ms time-window, showed familiarity recognition to negative stimuli was modulated by glucoregulatory control, with increased neurophysiological activity in poorer regulators following glucose. FN400 analysis, across the earlier 300-500 ms time-window, showed familiarity recognition to negative stimuli was modulated by glucoregulatory control, with increased neurophysiological activity in poorer regulators following glucose. As emotional stimuli may attract increased attention and evoke broader cognitive processing resources, more glucose is employed in this process. This suggests that poorer glucoregulators, may benefit from a glucose enhancement during increased demand, even though this is not to a level observable in behavioural data. This provides evidence that glucose preferentially targets individuals with challenged glucoregulation, and directly supports the findings of Messier et al., (2011). Messier suggested that, based on evoked levels of blood glucose, that there was a relationship between glucoregulatory control and performance on episodic memory tasks. Additionally, this may offer tentative support to the research of Parent et al., (1999) which found that emotionally arousing stimuli elevated blood glucose levels which may be preferentially advantageous to poorer, rather than better glucoregulators.

This chapter provides evidence that prior to the onset of clinical impairments in glucose regulation, changes in neural activity can be detected in a population of healthy young adults even in the absence of detectable decrements to episodic memory. Whereas the Messier et al., (2011) behavioural study failed to find support for the hypothesis that glucose ingestion would enhance the cognitive performance of poorer regulators, the ERP results from this chapter support that notion with glucose modulating the familiarity component of recognition memory. This FN400 finding provides evidence for the notion that the performance of poorer regulators would benefit from the glucose dose. One explanation which may elucidate this glucose facilitation in poorer regulators, is that those individuals may have presented (albeit to a minor degree) with depleted hippocampal interstitial glucose concentrations, and as such benefitted from the elevated blood glucose. Conversely, it may be because familiarity judgements rather than recollection judgements were affected in this earlier time-window, that we are seeing a more global enhancement due to increased cerebral glucose being made available to the frontal lobes by the ingested glucose.

This finding is a divergence from previous behavioural studies which suggested support for the hippocampus hypothesis, with glucose preferentially targeting recollection but with no enhanced familiarity (Sünram-Lea et al., 2008). On the other hand, the enhancement of familiarity discriminations found here does offer support for the Smith et al., (2009) study which previously found glucose modulating both recollection and familiarity. Greater amplitudes for 'familiarity' responses when the cognitive load was potentially increased by negative stimuli infers that a more global enhancement was elicited, offering support for the task demand theory. Enhancement of the FN400 component in the earlier latency window suggests that glucose is subserving this effect, potentially through early attentional processes.

Data for the 400-800ms time-window shows glucose enhancing LPC amplitudes for recollection, relative to familiarity discriminations for positive words. This is partial evidence in support of the task domain hypothesis. Glucose was seen to preferentially target recollection. However, this glucose facilitation was seen for positive stimuli and not, as predicted in response to neutral words which may suggest facilitation via emotionally charged increases in blood glucose levels. Glucose ingestion was also seen here to elicit higher LPC amplitudes for recollection but not familiarity which again concurs with the task domain view that glucose enhancement of verbal episodic memory is hippocampally mediated.

In terms of the lack of behavioural effects, an advantage of collecting ERP data alongside data collected from subjective remember/know discriminations is that ERPs are involuntary representations of these subjective behavioural discriminations. Whilst behavioural interpretations of participants' subjective remembering experience may be construed differently between individuals, the evidence from unconsciously created ERP waveforms provides an almost 'lie-detector' analogy to support the subjective process. Whilst Yonelinas (2002) suggested that the Remember/Know paradigm may be unreliable, it may be argued that these specifically relevant glucoregulation effects, which we have found to potentially occur prior to the manifestation of cognitive decrements. These effects may be highly nuanced and as such, only detectable by neurophysiological measures.

Support for the dual process model has also been shown in Chapter 4, with both ingested glucose and glucoregulatory control differentially modulating dissociations between recognition type. As these dissociations occurred in both the early time-window of the FN400 component data and the

later time-window of the LPC data this may be considered evidence to support the argument that recollection and familiarity are two functionally distinct memory processes.

In summary, the absence of glucoregulation and treatment effects in the behavioural data is commensurate with the view that in a cohort of healthy young adults, these early indications of cognitive effect are nuanced but potentially detectable in neurophysiological data. Slower behavioural responses to emotional compared to neutral stimuli suggests modulation of reaction times by varying cognitive demand across stimuli type rather than across the encoding phase as is often employed in dual tasking paradigms. Chapter 4 also provides distinct neurophysiological evidence to support the premise that acute glucose administration can enhance both the recollection and the familiarity components of recognition memory. The finding that poorer, but not better regulators benefitted from the glucose dose may provide tentative support for the view that acute ingestion of glucose is more commonly found to have a facilitative effect on individuals whose glucoregulatory control is compromised.

Whilst the outcomes of Chapter 4 did not provide clear direction in terms of the 'task domain' versus 'task demand' conundrum, it may be that task effort was not sufficiently demanding to exert an effective cognitive load as observed in dual tasking paradigms. Equally, it may also be the case that both of these mechanisms may be involved, there may have been benefits for hippocampal tasks and also benefits for other tasks if demands are high. Nonetheless the overarching finding of chapter 4, evidenced from the neurophysiological data, is that cognitive decrements can be seen at a very early stage of compromised glucoregulatory control. Results suggest that in a population of healthy young adults, pre-clinical levels of impaired glucoregulation can impact on recognition memory and as such, modulate neurophysiological responses to both recollection and familiarity.

5 The Impact of Elevated Type 2 Diabetes risk on Episodic Memory Processes and Inhibition: Comparing Neurophysiological, Glucoregulatory and Cardiovascular Factors in Non-diabetic, Healthy Young Adults Vs Potentially at Risk Young Adults.

5.1 Introduction

Chapter 4 findings showed that, whilst not seen in behavioural data, clear evidence was observed in the neurophysiological data that recognition memory is impacted by both glucose ingestion and glucoregulatory control. Ingested glucose was seen to increase activity in the P3 component relative to placebo during encoding. Relative to the two theories as to how glucose facilitation is subserved, chapter 4 found that glucose enhanced FN400 amplitudes for familiarity judgements of negative word recognitions made by poorer regulators relative to better regulators. This glucose enhancement of familiarity for negative words implies that global enhancement, resultant from the increased attentional resources required for processing emotional stimuli, was in play and suggests a demand facilitated glucose enhancement. As this glucose effect was only seen for poorer regulators, this is commensurate with the view that glucose more readily facilitates populations with challenged glucoregulatory control. In the later latency window of the LPC component glucose was seen to elevate amplitude responses for recollection judgements, lending support for the domain approach. Tentatively it may be concluded that, as effects for familiarity are occurring in the earlier time frame and recollection effects are occurring in the later time frame, that these outcomes support a dual-process memory system. Of the findings of chapter 4, perhaps the most pertinent to this chapter is the observation of differential neural activity between poorer and better glucoregulators. This tentatively suggests that in these data early neurological differences in the neural correlates of episodic memory were present between better and poorer regulators in this population.

Whilst the effect of glucoregulation has been shown in memory and executive functioning tasks, it has not yet been investigated in the context of healthy glucoregulators versus individuals who show elevated risk of developing poor glucoregulation. To assess this risk, a questionnaire will be designed which is sensitive to assessing T2DM risk in a population of healthy young adults. This will be adapted from purpose built risk assessment questionnaires which calculate individuals' risk for developing T2DM over the next 10 years (see section 5.2.5.3 for a full description). Differentially from Chapter 4, as smoking is a risk factor for insulin resistance (see section 1.3.5 for details of this),

and consequentially T2DM, smokers were not excluded from the present study. Risk score calculators are non-invasive, inexpensive, fast and can be used as a tool to identify those individuals who are at risk of developing T2DM. Those individuals found to be at risk can be directed toward interventions which will potentially prompt them to taking steps to prevent themselves from developing T2DM. This chapter will utilise these T2DM assessed risk scores to extend the concept of 'better' and 'poorer' glucoregulators.

Chapter 4 also investigated differences in heart rate beats per minute and, whilst there were no significant findings between the two glucoregulation groups, the heart rate of poorer glucoregulators was observed to be consistently higher than that of better regulators. In view of the lack of significant findings for the effects of glucoregulatory control or ingested glucose on heart rate in chapter 4 this chapter will move forward by investigating the heart rate variability within this construct (see section 1.4.1.1.1 for a more in depth description of HRV). The pertinence of HRV to this chapter is that in T2DM patients, low HRV is considered to be a risk factor of sudden cardiac death (Balkau et al., 1999; Kataoka et al., 2004) and in a diabetic population, low HRV was associated with excess mortality (Zentai et al., 2008). Previous research has been conducted to investigate the association between HRV and individuals' increased risk of potentially developing T2DM (Penčić-Popović et al., 2014). The authors found that non-diabetic individuals who were assessed by the Finnish Diabetes Risk Score (FINDRISC) as having increased T2DM risk, also had impaired heart rate variability, specifically those with higher risk scores were seen to have lower values for parasympathetic modulation (RMSSD, pNN50 and High Frequency (HF)) and also sympathetic modulation (Low Frequency (LF)). Chapter 5 will further this research by assessing HRV measures alongside T2DM risk and OGTT assessed measures of glucoregulation in both fasted state and following glucose ingestion.

Chapter 4 concluded from the Flanker task data that, whilst the conflict paradigm was indeed effective, the lack of evidence reflecting glucoregulatory control or ingested glucose may tentatively be a methodology issue. Previous research suggests that glucose enhancement of episodic memory only occurs in the context of high task difficulty (Kennedy & Scholey, 2000; Riby, et al., 2004; Scholey, MacPherson, Sünram-Lea, Elliott, Stough, & Kennedy, 2013; Scholey, Sunram-Lea, et al., 2009; Scholey, et al., 2001, 2006), (see section 1.5.2.6.1.1 for a detailed description of the task demand hypothesis). The lack of glucoregulation or treatment effects for the Flanker task data from chapters

3 and chapter 4 prompted the question as to whether this argument could be extrapolated to conflict tasks.

To augment this conjecture, the sustained attention to response (SART) task, a variation of the SART task employed by (Robertson et al., 1997), will be implemented in Chapter 5 (see section 1.5.2.3 for a description of conflict tasks). Robertson et al. suggested that lapses in attention leading to errors may be partly attributed to decrements in sustained attention. The SART task will focus on response inhibition and the demand on attentional resources will be increased by reducing the onscreen presentation time to 250 milliseconds compared to 500 milliseconds for the Flanker arrays. Additionally, the weighting ratio between Go (key press) and NoGo (no key press) trials will be changed from 3:1 for the Flanker tasks to 8:1 for SART, meaning that the increased habituation toward key presses will increase the likelihood of errors.

Poor glucose-regulation is implicated in aging and is a risk factor associated with diseases such as diabetes, dementia, Alzheimer's disease, and Parkinson's disease, all of which exhibit cognitive deficits such as memory loss. Glucose administration has been found to modulate these cognitive decrements (Smith, Riby, et al., 2011). Whilst it has been well documented that glucose ingestion can also enhance memory in healthy young adults, the processes which underlie this enhancement are unclear (for review articles see Messier, 2004; Riby, et al., 2004; Smith, Riby, et al., 2011).

Memory deficits are often comorbid with an underlying diagnosis of glucoregulatory disorders such as diabetes mellitus and previous research suggests that deficits such as the decrements in episodic memory seen in T2DM can be a risk factor for dementia (for a review see Sadanand et al., 2016). Moving forward from Chapter 4, this chapter will again investigate the role of glucoregulation on episodic memory in order to better understand the mechanisms and processes behind the memory decrements often found in populations such as individuals with T2DM. This chapter aims to further investigate the effect of glucoregulatory control and circulatory blood glucose levels on the 'recollection' (remembering) and 'familiarity' (knowing') components of the subjective experience of recognition memory. Chapter 5 additionally assesses participants for known risk factors associated with the potential for individuals to develop T2DM.

Chapter 5 aimed to elucidate the conflicting 'task-domain' versus 'task-demand' hypotheses. To account for the possibility that the cognitive demand of the episodic memory tasks was not sufficient

to evoke glucose facilitation, this chapter utilised a dual-tasking paradigm which manipulated demand by the inclusion of a high/low effort, secondary mouse tracking task during the encoding phases of the word recognition tasks.

Executive functioning has also been seen to be challenged by poor glucose regulation (Benton & Donohoe, 2004) and high demand cognitions such as inhibition and self-control are seen to deplete glucose levels faster than automatic cognitive processes (Fairclough & Houston, 2004; Gailliot et al., 2007). Decrements in inhibitive or self-control behaviours are seen in individuals with schizophrenia who show inappropriate behaviours, lack of self-control and impulsivity (Leung et al., 2014). To move forward from chapter 4, the SART task, which is a more stringent inhibition task is employed here as a 2-minute filler phase between the word recognition blocks and will pilot the secondary aim of the study, fully utilising the 'filler' periods.

As in chapter 4, this chapter will utilise ERPs to provide novel insights into the neural correlates of the cognitive processes supporting memory. The expectation of this chapter is that glucoregulation will modulate the ERP correlates of recognition memory when affective (emotionally valenced) stimuli are used, and cognitive demand is increased by the tracking task. Additionally, considering the findings of Chapter 4, it is expected that glucoregulatory control will have an impact on the neural activity associated with recognition memory processes with differences expected between the 'better' and 'poorer' glucoregulator groups. This chapter will investigate the relationships between glucoregulation, risk factors for developing poor glucoregulation (e.g., diabetes) and the effect of glucose administration.

The current chapter sought to augment current knowledge by identifying clear neurological evidence that glucoregulation and glucose administration differentially impact aspects of cognition. This chapter aims add to current knowledge by to establishing whether decrements in glucoregulatory control at a pre-clinical stage in healthy young non-diabetic adults are correlated with known T2DM risk factors, and additionally, whether these early decrements are potentially precursive of the glucoregulation related cognitive problems which are often found to be comorbid with T2DM. Investigating whether increased risk of poor glucoregulation in a sub clinical population, evokes differences in episodic memory and attentional resources. Identifying early markers of cognitive decline is useful as early interventions can be put in place prior to the onset of cumulative, and subsequently permanent damage to cognition.

Chapter 5 will also aim to gain new knowledge in terms of whether there is a relationship between glucoregulatory control and known T2DM risk factors, and the risk for the cardiovascular problems which are often comorbid with T2DM; specifically investigating whether this relationship is apparent in a cohort of young healthy adults. The impact of glucoregulation and glucose administration on measures of heart rate variability to explore whether early indications of cardiovascular problems, which are often comorbid with T2DM, are detectable in the current population.

Several research questions were addressed in this study. Establishing a link between glucoregulatory control and T2DM risk factors would be a useful and cost-effective strategy for identifying and recruiting potentially challenged populations. To investigate these objectives, the following research questions were posited : -

- Will there be a positive relationship between individuals glucoregulatory control and their T2DM risk score? It is expected that as circulatory blood glucose levels rise (as calculated by the iAUC from OGTT data), rising levels of T2DM risk will be seen.
- Is there a physiological response to emotional words during the encoding phase of recognition memory, which may be mediated by glucoregulatory control and/or glucose ingestion? It is suggested that glucose ingestion will elevate baseline heart rate in comparison to placebo. And additionally, that poorer regulators will have faster heart rate beats per minute than better regulators.
- Does fasted state heart rate variability differ between better and poorer glucoregulators. Poorer glucoregulators having lower heart rate variability than better regulators would be an early indication of a relationship between glucoregulatory control, and the cardiovascular challenges found in individuals with T2DM. Negative correlations between HRM measures and iAUC, T2DM risk scores, and baseline BPM; with measures of heart rate variability diminishing as the other factors increase. Heart rate variability metrics will differ between glucose and placebo ingestion.

- Will glucoregulatory control and/or ingested glucose impact on attentional resources during performance of the more stringent SART conflict task? If glucoregulatory control impacts on sustained attention, it would be expected that poorer regulators would have diminished accuracy and differential response speed performance compared to better regulators in the placebo

condition. If glucose enhancements are only seen for populations with challenged glucoregulatory control, then glucose ingestion would benefit poorer glucoregulators.

- Does glucoregulatory control or glucose ingestion impact on episodic memory, and additionally, is there an interaction between the two? If early cognitive decrements are present in the 'poorer' glucoregulatory group, and as glucose has been demonstrated to target compromised populations, glucose may have a facilitative effect on 'poorer' but not 'better' regulators.

- Is there evidence from behavioural word recognition data, of ingested glucose modulating episodic memory for emotional words? In turn, are there ERP amplitude differences between glucoregulation groups. If glucose is targeting the hippocampal domain, then recollection but not familiarity of neutral words would be influenced. Should there be a more global demand specific facilitation, then both recollection and familiarity of emotionally valenced stimuli may be influenced.

- Will the presence of a high-effort secondary task during encoding interact with glucose ingestion and/or glucoregulatory control and modulate the neurological correlates of recognition memory for emotional words? A facilitative effect of glucose following high demand would suggest support for the demand hypothesis. Conversely, differences following placebo would suggest support for a more global utilisation of circulating blood glucose.

- Will ERP components amplitude differ between better and poorer regulators? Glucoregulation differences would provide potential neurological evidence of early markers of the impact of glucoregulatory control. Additionally, treatment differences seen in ERP component amplitudes would suggest that glucose is modulating neurological responses to memory processes.

5.2 Materials and Method

5.2.1 Design

A randomised placebo controlled, double-blind two visit crossover design was employed. Analyses of both behavioural and neurophysiological data were conducted separately on encoding data, recognition accuracy data and subjective recognition data (Remember/Know paradigm). Apart from glucoregulation, which was a between- subjects variable, all other variables were within-subjects. The OGTT data was analysed via a one-way ANOVA and all other analyses were mixed factorial ANOVA.

5.2.2 Participants

Twenty-seven, self-reportedly healthy young adults (23 females, mean age 22.37 years, *SD 4.68)* (see Appendix 5.2 for demographic characteristics) took part in this study which was approved by the Staffordshire University Psychology Ethics Committee. Participants were recruited from the Staffordshire University student cohort. Prior to taking part in the study informed consent was obtained from all individual participants included in the study. Health and demographic screening, including the faculty blood-screening questionnaire, were completed to ascertain whether prospective participants met the exclusion/inclusion criteria of the study. Participants were screened for any food allergies which related to the treatments employed in the study and any glucoregulatory/metabolic disorders e.g., diabetes; individuals with heart rate disorders (Arrhythmias), or phenylketonuria were also excluded. All participants were asked to self-report whether they were in good health, free from prescription drugs (excluding contraceptives), over-the-counter medicines, illicit and recreational drugs. Differentially to chapter 4, smokers were not excluded as this chapter is exploring T2DM risk factors, which include smoking nicotine based products. Demographic and morphometric information was collected (BMI mean 25.8, *SD 6.24,* WHR 0.80, *SD 0.6*). For complete health screen and demographic data see Appendix 5.4 and Appendix 5.2 for an overview. Participants were assessed in terms of risk factors (see Appendix 5.3 for penalties associated with these factors) which potentially increase the likelihood of that individual going on to develop T2DM (see Appendix 5.4 for participants' risk scores). Participants attended three sessions; session one was to assess their glucoregulation and training was given for the cognitive tasks that were to be conducted during the two test visits. Before each visit participants fasted overnight for 12 hours during which time, they could only drink water. On completing the study students received £25

worth of high-street gift vouchers to compensate for travelling costs and those participants who were psychology students also received 15 SONA research points.

5.2.3 Blood Glucose Levels

On the first visit, participants' glucoregulation was assessed via a 75 g dose oral glucose tolerance test (OGTT) following a 12 hour overnight fast (water permitted). Finger prick blood samples were taken using a Roche Accutrend Plus diagnostic instrument and Accutrend Glucose Strips. Circulatory blood glucose levels were measured at baseline and then at 30, 60, 90 & 120-minute post glucose load. On study days blood glucose levels were measured at baseline, pre-test (10 minutes post-dose) and post-assessments (approximately 45 minutes post-dose). In Chapter 4 participants were assigned to better or poorer glucoregulation groups via a median split based on evoked levels of blood glucose (see section 4.2.3 details of the calculation of evoked levels). In view of the fact that the main focus of this chapter was to explore the relationship between glucose tolerance and the potential risk factors for T2DM it was thought prudent to calculate participant's iAUC which uses the OGTT five time-point blood glucose levels calculation to facilitate the median split, see Table 5.1 below for iAUC calculation formula using the Riemann's Sum method (see Sealey, 2006), Table 5.2 shows that the calculated iAUC measure for this particular participant was 919.80.

Table 5.1 Example of formulas for the iAUC calculation for one participant and calculated from five OGTT measures of circulating blood glucose levels taken after a 12 hour water only fast.

Column A (Dose/Time)	Column B (Timepoint)	Column C (BGL)	Column D (iAUC)
Baseline	0	3.16	=(C2+C3)/2*(B3-B2)
Dose+30	30	7.44	=(C3+C4)/2*(B4-B3)
Dose+60	60	9.5	=(C4+C5)/2*(B5-B4)
Dose+90	90	9.11	=(C5+C6)/2*(B6-B5)
Dose+120	120	6.06	
			=SUM(D2:D6)

Table 5.2 Example of iAUC calculation for one participant showing numerics.

Column A (Dose/Time)	Column B (Timepoint)	Column C (BGL)	Column D (iAUC)
Baseline	0.00	3.16	159.00
Dose+30	30.00	7.44	254.10
Dose+60	60.00	9.50	279.15
Dose+90	90.00	9.11	227.55
Dose+120	120.00	6.06	
			919.80

5.2.4 Treatments

Prior to the study drink orders were generated using a Latin Square, and then randomised and assigned to participant numbers. Treatments comprised of a 200ml drink with 20ml of Robinsons Sugar Free Orange Cordial to which had been added either 25g of glucose (www.myprotein.co.uk) or 5 saccharin 'Mini-Sweeteners' (www.Hermesetas.com). This is a standard drink, matched for sweetness and oral texture (Scholey, et al., 2001) used by similar studies in the literature. After drinks had been made, they were labelled by a disinterested third party who was not involved in the study; this ensured the double-blind status of the study. All drinks were prepared on the day prior to testing and were stored in sealed containers overnight in a refrigerator prior to serving. Whilst the participants were blind to their allocated treatment, they were fully informed as to the ingredients used in treatments to be consumed throughout the study.

5.2.5 Physiological Measures

5.2.5.1 ECG, Mean Heart Rate

Heart rate was monitored throughout using the Biopac MP36 Data Acquisition Unit. Electrodes were Vinyl Electrode Stress-Gel electrodes, EL503 for ECG, attached to participants' ankles and right wrist. Baseline heart rate for better and poorer glucoregulators was assessed during the 60 second calibration interval prior to task onset. During the encoding phase mean heart rate was measured over one, two and three seconds after presentation of each word, as such a measure of any effects of valence at the initial viewing of words.

5.2.5.1.1 Heart Rate Methodology

Heart rate was monitored throughout using electroencephalogram (ECG) data collected by a Biopac MP36 Data Acquisition Unit. Electrodes were Vinyl Electrode Stress-Gel electrodes, EL503 for ECG, attached to participants' ankles and right wrist. During the encoding phase mean heart rate was measured over one, two and three seconds after presentation of each word, as such, a measure of any effects of valence at the initial viewing of words. In chapter 5 glucoregulation effects of baseline resting heart rate were explored by recording heart rate during the 60 second calibration period prior to the commencement of the tasks. Prior to analysis all data was cleaned using the Biopac (Linton Instrumentation) guidance.

5.2.5.2 Heart Rate Variability

5.2.5.2.1 Heart Rate Variability Methodology

Participants' heart rate variability was assessed from data collected during the first 10 minutes of the encoding phase (see section 4.1.1.2.1 above for HRV methodology). HRV data was extracted from the ECG data, see 6.2.5.1 above. Analysis was conducted on a priori HRV time-domain and frequency-domain metrics found to have been associated with T2DM.

HRV data was extracted from the cleaned ECG data in the studies reported in the current chapter. Analysis was conducted on *a priori* HRV time-domain and frequency-domain metrics found to have been associated with T2DM, see Table 5.3. Participants heart rate variability was assessed from data collected during the first 10 minutes of the encoding phase, see Table 5.3 below for HRV parameters. Data was analysed using Biopac Systems 'Acknowledge' software. Multi-epoch HRV-Statistical analysis was conducted to extract data for the time-domain measures RMSSD, SDNN and %pNN50. Single-epoch HRV -Spectral analysis was conducted to extract data for the frequency domain measures of power in the Very Low Frequency Band, Low Frequency Band, High Frequency Band, and the Sympathetic-Vagal Balance (LF/HF).

To assess participants' fasted state HRV, analysis was conducted on data extracted from participants placebo visit data for time-domain and frequency-domain data. This data was used to assess glucoregulation differences (see section 5.4.4.1).

Table 5.3 Parameters suitable for assessing heart rate variability over a 10 minute period.

Parameter	Domain	Unit of Measurement	Description	Physiological Origin
RMSSD	Time-domain	ms	Root mean square of successive RR interval differences, associated with HF power/parasympathetic activity	Reflects parasympathetic activity
SDNN	Time-domain	ms	Standard deviation of all N-N intervals	Reflects vagal tone
pNN50	Time-domain	%	Percentage of successive 5 minute RR intervals that differ by more than 50%, associated with HF power/parasympathetic activity	Reflects vagal tone
VLF	Frequency-domain	ms^2	Power of the very low-frequency band (0.0033-0.04 Hz)	Represents the regulation of mechanisms related to thermoregulation and hormones.
LF	Frequency-domain	ms^2	Power of the low-frequency band (0.4-0.15 Hz)	Reflects an influence of a combination of sympathetic and parasympathetic branches of the ANS.
HF	Frequency-domain	ms^2	Power of the high-frequency band (0.15-0.4 Hz)	Relates to heart rate variations which react to cycles of respiration.
LF/HF	Frequency-domain	%	Ratio of LF power to HF power or sympathetic-vagal balance.	Indexes the interaction between sympathetic and parasympathetic activity.

Measurement of heart rate variability is a non-invasive method of investigation, and the outcomes give an indirect reflection of cardiac autonomic regulation (Silva-E-Oliveira et al., 2017). There are two common metrics used for assessing HRV (see Table 5.3 above for parameters). Firstly, 'time-domain' indices explore the variability in the measures of interbeat intervals, as such the intervals between successive heartbeats. Secondly, 'frequency-domain' indices quantify the percentage of total power into four frequency bands, one of which the very high frequency band (VHF) is commonly reported for rodent studies and as such is outside of the scope of this thesis. Chapter 5

seeks to explore the relationship between HRV and glucoregulation, to establish whether this is detectable at pre-clinical levels of poor glucoregulatory control. This would potentially lead to early detection of the cardiovascular issues which are often co-presenting with T2DM.

5.2.5.3 T2DM Risk Assessment

To assess participants' risk for developing T2DM a risk assessment was developed using three previously published and validated assessment tools. The first of these, which is used by Diabetes UK aimed to help individuals find out their risk of developing Type 2 diabetes was developed in collaboration with the University of Leicester and University Hospitals of Leicester NHS Trust. The second was the American Diabetes Association assessment which was adapted from a risk-scoring algorithm for undiagnosed diabetes (which is defined as fasting plasma glucose levels of 7.0 mmol/L) (Bang et al., 2009). The third was the Australian Type 2 Diabetes Risk Assessment Tool (AUSDRISK) which was developed by the Baker IDI Heart and Diabetes Institute on behalf of the Australian, State and Territory Governments as part of the COAG initiative to reduce the risk of type 2 diabetes. The questions used were principally from the Diabetes UK tool with additional questions found in the other two assessments about known T2DM risk factors such as smoking, physical activity added. Questions which were not relevant to the population of this study were omitted, for example age was not included as age does not become a risk factor until >49 years of age, personal diagnostic of high blood glucose was also omitted as this was one of the exclusion criteria for the study.

Questions were interspersed throughout the Health and Demographic Screen, see Appendix 5.3 and Appendix 5.4 for a list of questions and risk penalty scores.

5.3 Event Related Potentials Amplitude Analysis

For a detailed description of EEG methodology used in this chapter see section 4.2.6.1. The selection of ERP components was ascertained by *a priori* assumptions based on previous research in the glucose related recognition memory literature (see section 1.6.1. for a detailed description of these components). To further refine the latency windows of these components a global field power analysis was conducted on the data for each of the EEG related analyses. To accomplish this an average across all participants and all conditions was calculated and a global field power analysis was applied to each of the variable groups to identify peaks and latencies. ERP components were quantified by GFP analyses for encoding data, recognition data and subjective judgements of

recognition (Remember/Know) data. Peak latencies of components were further checked by separately conducting and comparing the GFPs for both treatment groups. These checks revealed that peak latencies of the FN400 and the LPC components for the glucose and placebo conditions of the remember/know data may differ. Should these latency windows differ significantly then separate latency windows for the glucose and placebo conditions would need to be implemented. Latency analysis was conducted to explore this further, see section 5.3.4.3.5.

5.3.1 Event Related Potentials

For a detailed description of ERP methodology used in this thesis see section 4.2.6.1. The ERP components employed in the experiment, which have been identified in the glucose and recognition memory *a priori* literature, as are described in section 1.6.1.

5.3.2 Cognitive Assessments

On study days cognitive task assessments were presented in four blocks, each with identical formats in terms of task content. Task demand, however, was manipulated on half of the blocks, by the addition of a mouse tracking task (see section 5.3.2.2 below) during the encoding phase of the high demand blocks. Across the 2 study sessions eight different word lists were used and no words were interchangeable between blocks and visits.

5.3.2.1 Word Display Encoding Phase

Four hundred and eighty words were selected from 'Affective Norms for English Words' (Bradley & Lang, 1999). The words were randomised for each participant into 4 lists of 60 of neutral valence and 4 lists of 60 words of emotional valence (half negative/half positive). In each word list, 30 were designated as 'old' and are displayed during the initial word display; the remaining 30 are 'novel' and are displayed only in the recognition phase of the visit. Eight different word lists were used throughout the two study visits, each comprising of only neutral or emotional words (negative and positive) to ensure that there was no carry over effect of emotionality. Each word list was randomised for each participant. Participants saw a different word set at each assessment. One-way ANOVAs were employed prior to data collection to ascertain that the mean valences of negative, neutral, and positive words were significantly different and, that there was no significant difference across the eight word lists. For the encoding phase 30 each neutral or emotional (15 positive and 15 negative) words were randomly presented on the centre of the screen for 2 seconds with a 1 second

interstimulus delay during which time a fixation cross appeared on the centre of the screen. Words shown in the encoding phase were classed as 'old' words.

5.3.2.2 Dual-Task

To manipulate cognitive demand a mouse tracking dual-task (high demand) was used to increase cognitive demand for two of the four blocks of cognitive tasks performed at each visit during the encoding phase of the word recognition task. Participants were instructed to use the mouse pointer to track a green asterisk which moved around the screen in a random pattern (Naveh-Benjamin et al., 2005) while at the same time attending to the words which were presented on the screen. The distance between the target and the cursor was computed every 100 ms and the result converted to a 'tracking cost' score in pixels.

5.3.2.3 Sustained Attention to Response Task (SART)

The inhibition task used as a filler task between word blocks is a variation on the SART employed by (Robertson et al., 1997). It is a computerised attention task with participants being required to respond as quickly as possible with a spacebar press to a frequent target stimulus, the numbers 1,2,4,5,6,7,8 and 9, which were presented individually and randomly in the centre of the screen. The stimuli were black, and these were presented centrally on a white screen. When presented with the infrequent non-target stimuli, the number '3', participants were instructed to withhold responses. There was a total of 315 trials presented in 7 blocks of 45 trials in each block and overall, the ratio of 'GO' trials to 'NO GO', was weighted disproportionally to 'GO' responses at a ratio of 8:1 . Each digit was on screen for 250 milliseconds followed by a 900 millisecond fixation mask during which a response could be made. To discourage hesitancy participants were instructed to make rapid responses as 'time-outs' would be logged as incorrect responses.

5.3.2.4 Word Recognition

Behavioural assessments for word recognition were based on percentage accuracy of correct recognitions of previously studied 'old' words and correct rejections of unseen 'new' words. The recollection and familiarity components of recognition memory were assessed using the subjective 'remember/know' paradigm (Tulving, 1985). At the beginning of each word recognition block participants were given an overview of the processes. For the recognition phase participants were shown the 30 previously studied words randomly displayed with 30 novel words (distractors not seen

during the encoding phase) and asked if they recognised the word from the related word list. If the participant responded, 'yes' they were then asked to quantify their subjective remembering experience by selecting 'J' (Remember) 'K' (Know).

5.3.3 Procedure

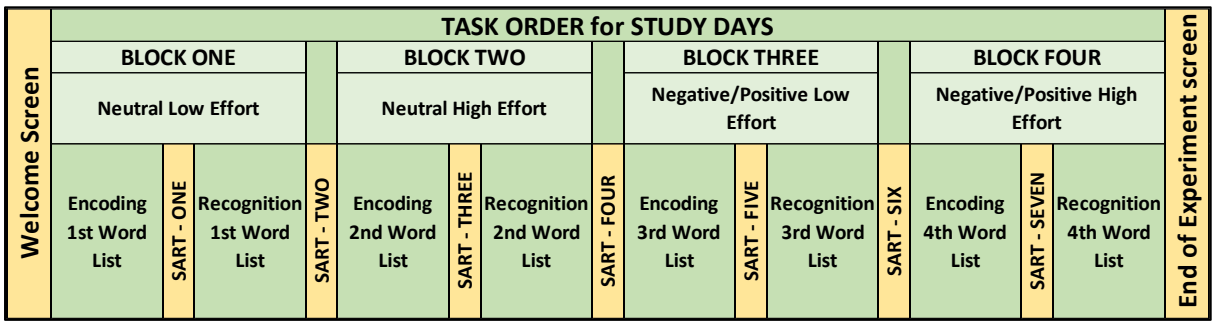
The purpose of the first session was to conduct an Oral Glucose Tolerance Test (OGTT) and give participants verbal and on-screen task training, they were given a choice of starting time and attended the laboratory between 8.00 am and 9.30 am after a 12 hour fast. Subsequent study day visits, after a minimum of a 2-day washout period, were time matched to their starting time for the initial visit to ensure uniformity. The researcher ensured participants were clear on what was expected of them, checked the screening forms to ensure the participants met the inclusion criteria and invited questions. Participants' height, weight, waist, and hip measures were taken by the researcher and recorded on the health screen form, for all demographic details see Appendix 5.4 for the health and demographic screen with associated T2DM risk assessment scores.

The OGTT was conducted to assess individuals' glucoregulation and the outcomes of this enabled a median split which allocated participants to either 'better' or 'poorer' glucoregulator groups. A practice battery of tests with verbal instruction, as well as task related onscreen instructions, was performed to train participants on each of the tasks that were used during the study day visits. The practice battery comprised of 12 repetitions of each of the cognitive tasks lasted for approximately 15 minutes and was performed during one of the 30-minute waiting times between OGTT blood sampling. No data was collected from these practice sessions. Participants were given an overview of the procedure for the study days, shown the laboratory and the equipment to be used and given details about hair washing/showering facilities.

On study day visits participants attended individually and were seated in front of a computer in the EEG laboratory. As this was a within-groups comparisons were made across conditions rather than do a baseline assessment at each visit. The rationale for this was that as the sessions already lasted for a minimum of 1.5 hours, taking into account the capping process, blood sampling and drink consumption and absorption, adding a further 45 minutes of sitting still because of EEG and ECG electrodes would have been tiring and uncomfortable for participants. Additionally, and importantly the electrical impedances of the EEG electrodes, which were all kept to a minimum, tend to drift with time and movement, and as this would all be reflected in the post-treatment data, comparison

between baseline and post-treatment would not have been robust. Comfort and wellbeing of participants was also a consideration. The researcher was in an adjoining control room and there was two-way microphone/speaker communication between the two the rooms throughout the session. A non-recording web camera was also directed at the participants' computer screen so that the researcher could monitor progression. The timeline of study visits can be seen in Figure 5.1 below. After the equipment had been removed participants were offered hair washing facilities.

Figure 5.1 A schema of tasks on study day visits



5.3.4 Statistical Analyses

5.3.4.1 Data Cleaning

Data was screened and cleaned prior to analysis. Where non-sensible values, missing data or outliers were found these were omitted from the analyses using listwise deletion. Datasets were checked for assumptions of mixed-groups ANOVA, as such, independence of scores, normal distribution, homogeneity of variance and sphericity where the within-groups variables had 3 or more levels.

5.3.4.2 Word Recognition Behavioural Data

For the word recognition task old/new discriminations were analysed in terms of accuracy and recognition response time via five-way mixed factorial (Treatment (2) x Demand (2) x Word Type(2) x Valence(3) x Glucoregulation(2)) ANOVA.

5.3.4.3 ERP Amplitude Analysis

As EEG data is rarely homogenous, to compensate for these violations in the analysis of repeated measures ANOVA designs, Greenhouse-Geisser corrections were applied to all ERP analyses to

ensure that type 1 error rates were not inflated by the potential lack of homogeneity found in EEG data (Picton et al., 1995; Picton et al., 2000; Greenhouse & Geisser, 1959) .

5.3.4.3.1 Word Recognition Encoding data.

Encoding analyses were conducted for four ERP components which are suggested to be associated with sensitivity to the emotional, attentional and recognition aspects of visual word processing: specifically, the P1, the N1, the P3 and the LPC components. Determination of the relevant time windows was based on *a priori* research and these time windows were then refined via the calculation of global field power (see Figure 5.2 below). Observation of the P1 positive going component was from 60 to 130ms post stimulus presentation, the N1 negative going component over the 130 to 220ms time window; the P3 positive going component over the 210 to 330ms time window and the LPC positive going component over the 540 to 780ms time window. Mixed factorial ANOVAs were conducted on data from 3 anterior and 3 posterior electrodes (F3, Fz,F4 and P3, Pz and P4) Anterior and posterior electrode selections provided two levels of a region variable; right, left and midline comprised the three levels of a hemisphere variable. Thus, a six-way mixed factorial ANOVA (Treatment (2) x Demand (2) x Region (2) x Valence (3) x Hemisphere (3) x Glucoregulation (2)) was conducted.

Figure 5.2 Encoding data positive peaks identified by GFP analysis and representing components and latencies across averaged epoch.

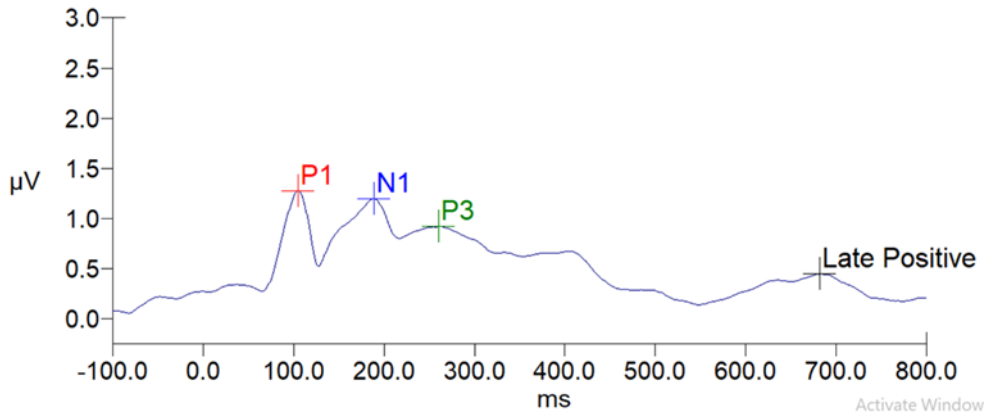
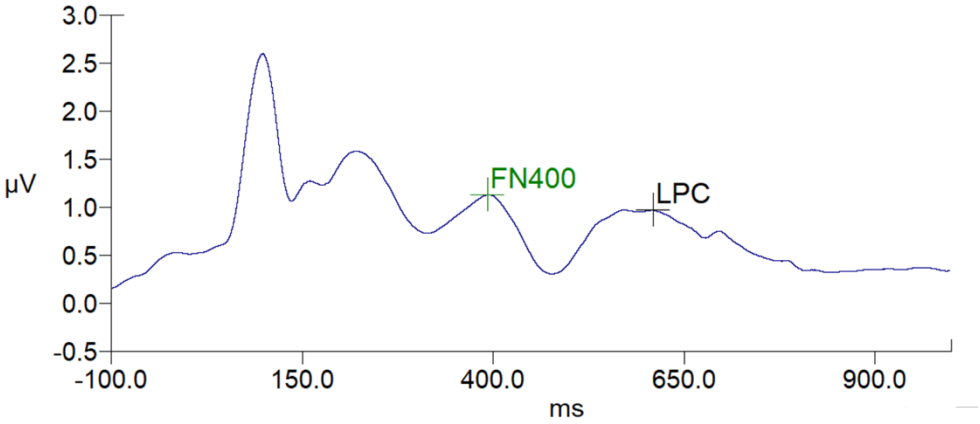


Figure 5.3 Positive peaks of recognition data identified by GFP analysis and representing components and latencies across averaged epoch.



5.3.4.3.2 Word Recognition Old/New Data

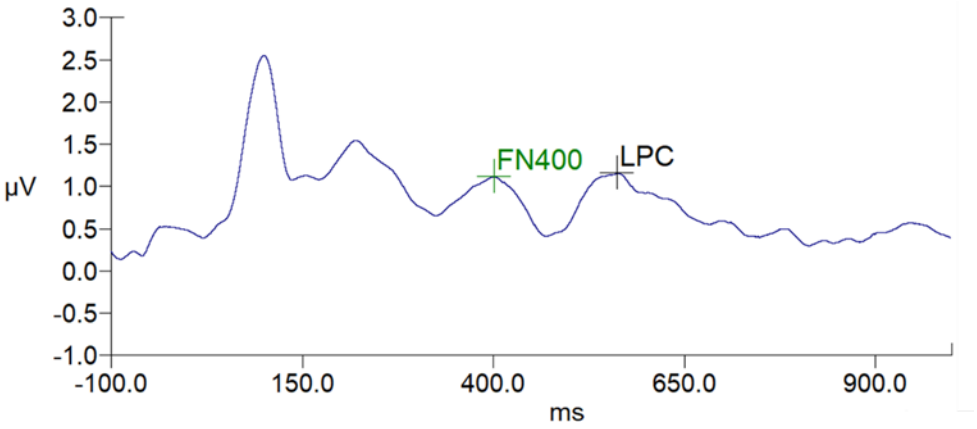
Conventionally the FN400 component old/new effect is investigated in the 300 – 500ms time window and is believed to reference familiarity and at anterior electrode sites. In the 400 – 800ms time window LPC component is thought to reference recollection at the posterior electrodes. The chosen time windows were based on *a priori* research and then refined by the calculation of global field power (see Figure 5.3 below). Subject to these refinements the FN400 analyses were conducted in the 310 to 480ms time window and the LPC analyses over the 470 to 780ms time window. Analyses was via mixed factorial ANOVAs conducted on data from 3 anterior and 3 posterior electrodes (F3, Fz,F4 and P3, Pz and P4). As the work of this thesis is an exploratory investigation of glucoregulation differences, both anterior and posterior regions were included in each analysis to ascertain whether there were differences between the two regions. As before, anterior, and posterior electrode selections provided two levels of a region variable; right, left and midline comprised the three levels of a hemisphere variable. Thus, a seven-way (Treatment (2) x Demand (2) x Region (2) x Recognition Type (2) x Valence (3) x Hemisphere(3) x Glucoregulation (2) was conducted for both the FN400 component and the LP component.

5.3.4.3.3 Word Recognition Remember/Know

ERP data relative to participants' subjective experience of remembering or knowing correctly recognised old words. Analysis investigating the FN400 component was conducted in the 320 to

480ms time window and the LP component was explored in the 450 to 780ms time window. The chosen time windows were based on *a priori* research and then refined by the calculation of global field power (see Figure 5.4 below). Both analyses were via mixed factorial ANOVAs conducted on data from 3 anterior and 3 posterior electrodes (F3, Fz,F4 and P3, Pz and P4). Anterior and posterior regions were included in each analysis to ascertain whether there were differences between the anterior and posterior electrode sites. As before, anterior, and posterior electrode selections provided two levels of a region variable; right, left and midline comprised the three levels of a hemisphere variable. Data was subjected to mixed factorial seven-way (Treatment (2) x Demand (2) x Region (2) x Recognition Type (2) x Valence (3) x Hemisphere(3) x Glucoregulation (2) ANOVAs.

Figure 5.4 Remember/Know data positive peaks identified by GFP analysis and representing components and latencies across averaged epoch.



5.3.4.3.4 ERP Component Latency Ranges

Table 5.4 below shows the ERP components for each of the data analyses, with their respective latency ranges on which analysis was conducted.

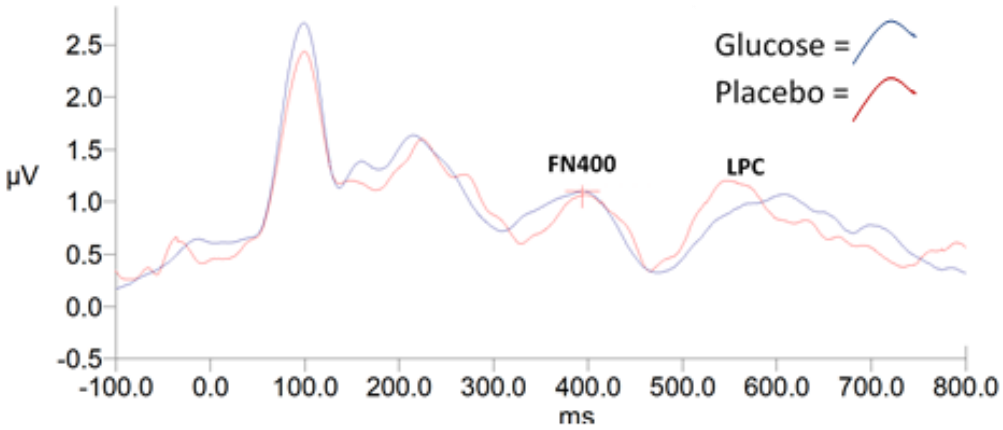
Table 5.4 ERP components selected from *a priori* research, refined with global field power and latency analysis checks for the subjective judgement analyses.

Analysis	Component	Latency Range
Encoding	P1	60 – 130 ms
	N1	130 – 220 ms
	P3	210 – 330 ms
	Late Positive Component	540 – 7800 ms
Recognition	FN400 – Old words / New words	310 – 480 ms
(Accuracy)	Late Positive – Old words / New words	470 – 780 ms
Recognition	FN400 - Remember / Know	320 – 480 ms
(Subjective Judgements)	Late Positive - Remember / Know	450 – 700 ms

5.3.4.3.5 ERP Latency Checks

Following the GFP analysis to refine the *a priori* assumptions of the component latencies for each of the data sets (encoding, recognition and the Remember/Know subjective recognitions). Further checks were made to ensure that the latencies of the glucose and placebo condition GFPs were not significantly different. Following the comparisons of glucose and placebo condition GFPs it appeared that the latencies of the FN400 and the LPC components differed, see Figure 5.5 below. To establish whether this issue was significant, in which case separate latency windows would be used to define the glucose and placebo treatment conditions, latency analysis was conducted on the FN400 and LPC components. Peak latency was identified across these components within the two treatment groups (glucose/placebo) at each of the 6 electrodes previously identified by *a priori* recognition memory/glucoregulation research (F3, Fz, F4, P3, Pz, P4). For each of the components Treatment: glucose/placebo) x 2(Region: anterior/posterior) x 3(Hemisphere: left/midline/right) mixed factorial ANOVAs were conducted to identify any main effects or interactions. As EEG data is rarely homogenous, to compensate for these violations in the analysis of repeated measures ANOVA designs, Greenhouse-Geisser corrections were applied to all ERP analyses to ensure that type 1 error rates were not inflated by the potential lack of homogeneity found in EEG data (Picton et al., 1995; Picton et al., 2000; Greenhouse & Geisser, 1959).

Figure 5.5 Comparison of glucose and placebo GFP averages for the word recognition subjective judgements ERP component latency checks.



5.3.4.3.5.1 FN400 Latency Analysis for Remember/Know Data

Analysis of the 2 x 2 x 3 mixed factorial ANOVA did not reveal any significant interactions or main effects (see Table 5.5 below), indicating that for the Remember/Know FN400 component there was no significant latency difference between the glucose and placebo treatment conditions and as such the amplitude analysis of the same GFP refined latency window was appropriate for analysis of this component.

Table 5.5 FN400 component latency analysis for subjective recognition judgements in the 320 - 480 ms time window. ANOVA F values, degrees of freedom significance levels and effect size (r) for latency interactions and main effects.

Main Effect/ Interaction	df	F	p value	r
Region x Hemisphere x Treatment	(2,98)	0.528	0.590	0.04
Hemisphere x Treatment	(2,96)	0.691	0.50	0.05
Region x Treatment	(1,49)	1.173	0.284	0.11
Region x Hemisphere	(2,98)	0.528	0.590	0.04
Treatment	(1,49)	1.588	0.214	0.07
Region	(1,49)	3.258	0.077	0.18
Hemisphere	(1.95,96)	2.744	0.071	0.09

5.3.4.3.5.2 LPC Latency Analysis for Remember/Know Data

Analysis of the 2 x 2 x 3 mixed factorial ANOVA revealed a significant main effect of hemisphere (see Table 5.6 below) however, Bonferroni adjusted pairwise comparisons were all non-significant. In view of this, and with all other interactions and main effects being non-significant, the Remember/Know LPC component was not showing significant latency difference between the glucose and placebo treatment conditions. As such, amplitude analysis of the same GFP refined latency window was appropriate for analysis of this component.

Table 5.6 LPC component latency analysis for subjective recognition judgements in the 450 - 780 ms time window. ANOVA F values, degrees of freedom significance levels and effect size (r) for latency interactions and main effects.

Main Effect/ Interaction	df	F	p value	r
Region x Hemisphere x Treatment	(2,94)	3.082	0.051	0.09
Hemisphere x Treatment	(2,96)	0.024	0.976	0.01
Region x Treatment	(1,48)	0.645	0.426	0.14
Region x Hemisphere	(2,94)	2.213	0.116	0.08
Treatment	(1,48)	0.024	0.877	0.01
Region	(1,48)	2.312	0.135	0.14
Hemisphere	**(1.997,96)**	**3.343**	**0.04**	**0.12**

5.3.4.3.5.3 Remember / Know Data Capture Issue

ERP analyses of the subjective remember/know data was not possible because there were insufficient trials of subjective responses; due to the multiple choice nature of the remember or know question of participants' subjective experience of recognition.

5.3.5 Summaries

Summaries of measures are included following the results for each of the mood and physical state assessments and the cognitive tasks results.

5.4 Physiological Results

5.4.1 Demographic and Physiological Means Table

See Table 5.7 for participant demographics and OGTT blood glucose levels.

Table 5.7 Demographic, oral glucose tolerance test blood glucose data, baseline heart rate and heart rate variability means and SEMs of the better and poorer regulators for males and females.

Measure	Better regulators				Poorer Regulators			
	Males		Females		Males		Females	
	Mean	*(SEM)*	Mean	*(SEM)*	Mean	*(SEM)*	Mean	*(SEM)*
Age (years)*	22.50	(2.50)	22.27	(1.26)	26.50	(6.50)	21.75	(1.40)
Education (years)*	17.00	(3.00)	16.64	(0.74)	15.00	(1.00)	15.17	(0.42)
BMI (kg/m^2) #	26.22	(1.25)	23.73	(1.06)	20.76	(0.46)	28.46	(2.31)
Waist/Hip Ratio (W/H) #	0.84	(0.03)	0.77	(0.01)	0.77	(0.05)	0.82	(0.02)
Fasting Glucose (mmmol/l)	4.56	(<0.00)	4.58	(0.10)	4.95	(0.06)	4.68	(0.12)
30 Minute Glucose (mmmol/l)	6.61	(0.83)	6.55	(0.31)	7.58	(0.75)	8.73	(0.27)
60 Minute Glucose (mmmol/l)	5.53	(1.14)	5.96	(0.28)	8.23	(0.05)	8.27	(0.30)
90 Minute Glucose (mmmol/l)	5.78	(0.50)	5.18	(0.23)	5.67	(0.89)	6.58	(0.29)
120 Minute Glucose (mmmol/l)	5.75	(0.14)	5.48	(0.24)	5.75	(0.42)	6.10	(0.20)
AUC	692.10	(76.23)	681.51	(17.01)	804.59	(7.92)	869.10	(18.38)
Baseline Heart Rate (BPM)	61.89	(3.33)	67.37	(2.33)	65.34	(3.89)	69.81	(1.99)
HRV / RMSSD (msecs)	61.75	(5.5)	63.44	(10.90)	58.68	(14.84)	59.65	(11.17)
HRV / SDSD (msecs)	61.75	(1.37)	63.44	(10.90)	58.69	(14.84)	59.65	(11.17)
HRV / pNN50 (msecs)	40.86	(5.96)	34.61	(5.69)	33.70	(11.37)	33.15	(5.93)
HRV / Sypathetic-Vagal Balance	1.14	(0.11)	2.44	(0.84)	2.19	0.31)	2.11	(0.73)

Note: * = participant' self-report measures; # = measures taken by researcher

AUC = area under the response curve of blood glucose levels

5.4.2 Blood Glucose Levels, Glucoregulation and T2DM Risk

5.4.2.1 Oral Glucose Tolerance Test

See Table 5.8 below for better and poorer glucoregulation groups OGTT means and SEMs (groups defined by a median split of iAUC measures of circulatory blood glucose levels).

Table 5.8 Oral Glucose Tolerance Test. Means, SEMs and significant effects are indicated (*Gluc = Glucoregulation Group. **p<.005*p<0.001,*)**

Outcome	Timepoint	Glucoregulation Group	N=	Mean and SEMs			Significant Effects
				Means	±	SEM	
OGTT Blood Glucose Levels	Baseline	Better	13	4.58	±	0.31	-
		Poorer	14	4.72	±	0.41	
	30 minutes	Better	13	6.56	±	0.99	Gluc ***
		Poorer	14	8.56	±	1.00	
	60 minutes	Better	13	5.89	±	0.98	Gluc ***
		Poorer	14	8.26	±	0.96	
	90 minutes	Better	13	5.27	±	0.77	Gluc **
		Poorer	14	6.45	±	1.05	
	120 minutes	Better	13	5.52	±	0.74	-
		Poorer	14	6.05	±	0.67	

Analysis of blood glucose levels over the two hour OGTT, as would be expected, indicated a normal response curve of overall mean blood glucose levels for a cohort of healthy young adults (see Table 5.7 above for means and SEMs), however the one-way ANOVA revealed that there were significant differences between the blood glucose levels of better compared to poorer glucoregulators at 30, 60 and 90 minutes post dose (see Table 5.9 and Figure 5.6). A one-way ANOVA revealed a significant difference between the median split (based on iAUC) designated groups ($F(1,25) = 55.140$, $p < .001$, $r = 0.83$), with significantly healthier glucoregulation seen in the 'better ' group (Mean = 683.14, SEM = 16.72) compared to the 'poorer' group (Mean = 859.88, SEM = 16.88), see Figure 5.7 below.

Table 5.9 OGTT one-way ANOVAs showing differences at five time points between better and poorer glucoregulator groups. ANOVA F values, degrees of freedom, significance levels and effect sizes are shown.

Time Point	df	F	p value	r
Baseline	(1,25)	0.991	0.329	0.20
Dose + 30	(1,25)	27.476	<0.001	0.72
Dose + 60	(1,25)	39.965	<0.001	0. 20
Dose + 90	(1,25)	10.878	0.003	0.55
Dose + 120	(1,25)	3.789	0.063	0.36

Figure 5.6 OGTT. Blood glucose level differences between glucoregulation groups at OGTT Time points. Figure key shows pairwise comparisons and significance levels. ***(*p< .05; **p< .01).*** **Bars show standard error.**

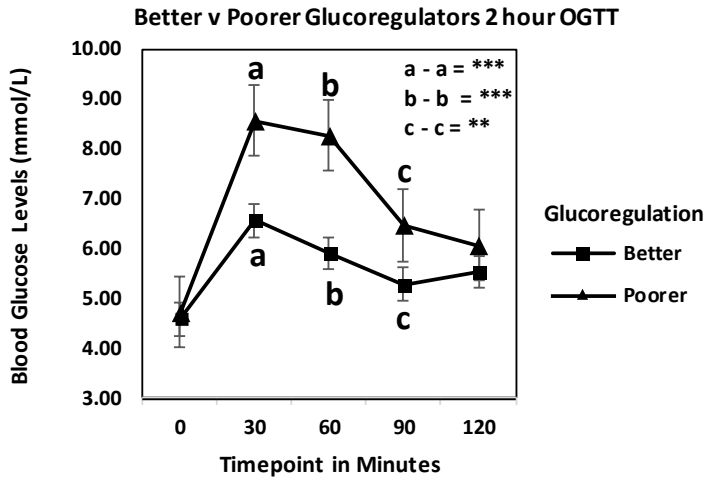
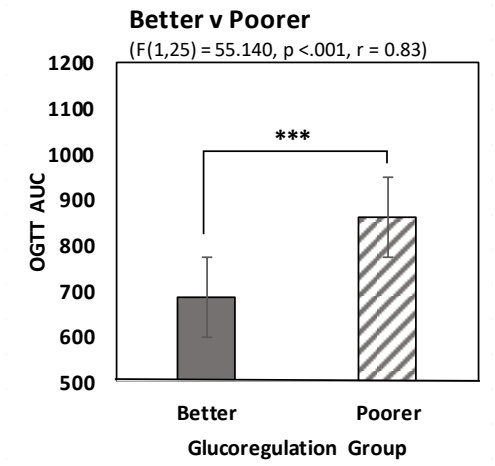


Figure 5.7 Comparison of glucoregulation groups as assigned via the AUC median split. ***(***p< .001).*** **Bars show standard error.**



Prior to the main analysis, One-way ((2) Glucoregulation) ANOVAs conducted on baseline scores of test visit blood glucose levels found that there were no significant differences between the glucoregulation groups for the glucose test visits ($F(1,25) = 3.085$, $p = .091$, $r = 0.33$), at baseline on the placebo visits blood glucose levels were higher ($F(1,25) = 8.457$, $p = .007$, $r = 0.50$) for poorer regulators (Mean = 4.89; SEM = 0.13) compared to better regulators (Mean = 4.40; SEM = 0.11).

Means, SEMs and significant effects and interactions for the test visit blood glucose levels primary ANOVA can be found in Table 5.13 below.

Table 5-10 Test Visit Blood Glucose Levels. Means, SEMs and significant effects and interactions are indicated (Gluc = Glucoregulation Type, Ti = Time, Tr = Treatment; **p<0.01, ***p<0.001).

Outcome	Timepoint	Glucoregulation	N=	Glucose			Placebo			Significant Effects and Interactions
				Means	±	SEM	Means	±	SEM	
Blood Glucose Levels	Baseline	Better	13	4.52	±	0.15	4.44	±	0.13	Ti *** Tr*** Ti x Tr *** Gluc **
		Poorer	14	4.89	±	0.14	4.89	±	0.12	
	Pre-Tasks	Better	13	5.40	±	0.31	4.33	±	0.14	
		Poorer	14	5.92	±	0.29	4.65	±	0.13	
	Post-Tasks	Better	13	6.30	±	0.33	4.21	±	0.13	
		Poorer	14	7.09	±	0.31	4.59	±	0.12	

For the mixed factorial ANOVA conducted on test visit data the primary three-way time x treatment x glucoregulation interaction was non-significant ($F(2,48) = 0.458$, $p = 0.635$, $r = 0.01$). Significant main effects and interactions can be seen below in Table 5.14.

Table 5-11 Test Visit Blood Glucose Levels. Three-way ANOVA F values, degrees of freedom, significance levels and effect sizes for interactions and main effects are shown.

Main Effects and Interactions	df	F	p value	r
Time x Treatment	(2,48)	36.374	<0.001	0.55
Glucoregulation Type	(1,24)	8.775	0.007	0.05
Time	(2,48)	20.505	<0.001	0.07
Treatment	(1,24)	103.418	<0.001	0. 12

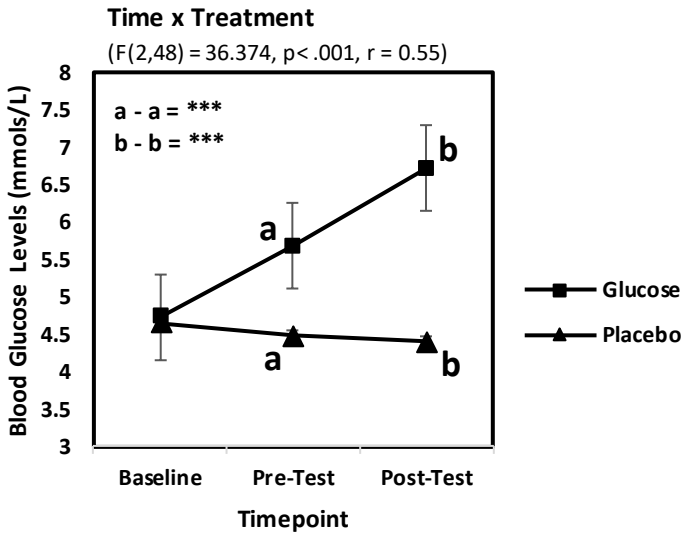
For the time x treatment interaction ($F(2,48) = 36.374$, $p<.001$, $r = 0.55$), (see Table 5.14 above and Table 5.15 below for interaction means and SEMs), significant pairwise comparisons showed that, as expected, at baseline there was no significant difference between the glucose condition (Mean 4.707, SEM 0.099) compared to the placebo condition (Mean 4.662, SEM 0.085). However, following the glucose dose; at pre-test blood glucose levels were significantly higher for the glucose condition

(Mean 5.662, SEM 0.210) relative to the placebo condition (Mean 4.490, SEM 0.096), ($t(24) = 6.141$, $p<0.001$). Also, at post-test blood glucose levels were higher following glucose (Mean 6.694, SEM 0.225) compared to placebo (Mean 4.403, SEM 0.091), ($t(24) = 9.351$, $p<0.001$), see Figure 5.9 below.

Table 5-12 Test Visit Blood Glucose Levels. Means and SEMs depicting the treatment x time interaction.

Treatment	Time	Mean	±	SEM
Glucose	Baseline	4.707	±	0.099
	Pre-Tasks	5.662	±	0.21
	Post-Tasks	6.694	±	0.225
Placebo	Baseline	4.662	±	0.085
	Pre-Tasks	4.49	±	0.096
	Post-Tasks	4.403	±	0.091

Figure 5.8 Test Visit Blood Glucose Levels. Pairwise comparisons for the time x treatment interaction. Figure key shows pairwise comparisons and significance levels. (*p<.001)*. Bars show standard error.**



The main effect of glucoregulation type ($F(1,24) = 8.775$, $p = 0.007$, $r = 0.05$) showed that overall better regulators had lower blood glucose levels (Mean 4.866, SEM 0.117) compared to poorer regulators (Mean 5.340, SEM 0.109).

5.4.2.1.1 Summary of Blood Glucose Levels and Glucoregulation Results

The oral glucose tolerance tests conducted on all participants facilitated the forming of two groups based on their incremental iAUC for blood glucose response over the OGTT, as such 'better' and 'poorer' regulators. The glucoregulation of the groups was found to be significantly different (see Figure 5.6 and Figure 5.7) with better regulators having lower levels of circulatory blood glucose levels. Analysis of blood glucose levels taken on study days confirmed that participants glucoregulation conformed to the expected differences following glucose or placebo treatments. Analysis of test visit baseline blood glucose levels found that there was a significant difference in baseline measures for the placebo visit, with poorer regulators having slightly high levels of blood glucose.

5.4.2.2 Test Visit Blood Glucose Levels

Prior to the main analysis, One-way ((2) Glucoregulation) ANOVAs conducted on baseline scores of test visit blood glucose levels found that there were no significant differences between the glucoregulation groups for the glucose test visits ($F(1,25) = 3.085$, $p = .091$, $r = 0.33$), at baseline on the placebo visits blood glucose levels were higher ($F(1,25) = 8.457$, $p = .007$, $r = 0.50$) for poorer regulators (Mean = 4.89; SEM = 0.13) compared to better regulators (Mean = 4.40; SEM = 0.11).

Means, SEMs and significant effects and interactions for the test visit blood glucose levels primary ANOVA can be found in Table 5.13 below.

Table 5.13 Test Visit Blood Glucose Levels. Means, SEMs and significant effects and interactions are indicated (Gluc = Glucoregulation Type, Ti = Time, Tr = Treatment; **p<0.01, ***p<0.001).

Outcome	Timepoint	Glucoregulation	N=	Glucose			Placebo			Significant Effects and Interactions
				Means	±	SEM	Means	±	SEM	
Blood Glucose Levels	Baseline	Better	13	4.52	±	0.15	4.44	±	0.13	Ti *** Tr*** Ti x Tr *** Gluc **
		Poorer	14	4.89	±	0.14	4.89	±	0.12	
	Pre-Tasks	Better	13	5.40	±	0.31	4.33	±	0.14	
		Poorer	14	5.92	±	0.29	4.65	±	0.13	
	Post-Tasks	Better	13	6.30	±	0.33	4.21	±	0.13	
		Poorer	14	7.09	±	0.31	4.59	±	0.12	

For the mixed factorial ANOVA conducted on test visit data the primary three-way time x treatment x glucoregulation interaction was non-significant (F(2,48) = 0.458, p = 0.635, r = 0.01). Significant main effects and interactions can be seen below in Table 5.14.

Table 5.14 Test Visit Blood Glucose Levels. Three-way ANOVA F values, degrees of freedom, significance levels and effect sizes for interactions and main effects are shown.

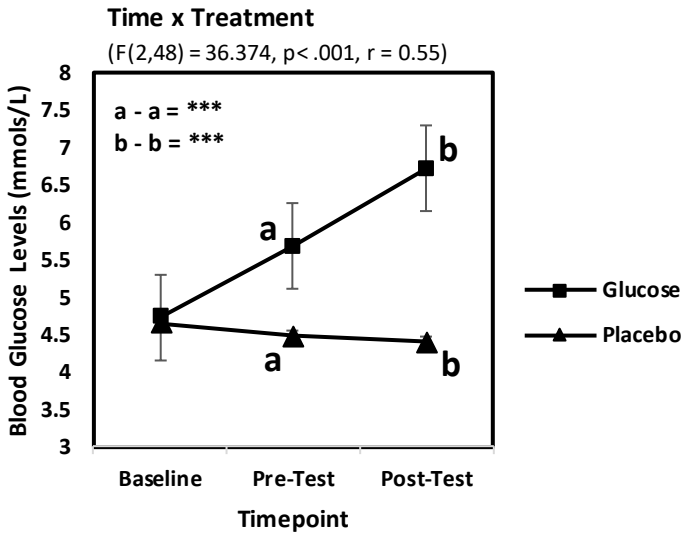
Main Effects and Interactions	df	F	p value	r
Time x Treatment	(2,48)	36.374	<0.001	0.55
Glucoregulation Type	(1,24)	8.775	0.007	0.05
Time	(2,48)	20.505	<0.001	0.07
Treatment	(1,24)	103.418	<0.001	0. 12

For the time x treatment interaction (F(2,48) = 36.374, p<.001, r = 0.55), (see Table 5.14 above and Table 5.15 below for interaction means and SEMs), significant pairwise comparisons showed that, as expected, at baseline there was no significant difference between the glucose condition (Mean 4.707, SEM 0.099) compared to the placebo condition (Mean 4.662, SEM 0.085). However, following the glucose dose; at pre-test blood glucose levels were significantly higher for the glucose condition (Mean 5.662, SEM 0.210) relative to the placebo condition (Mean 4.490, SEM 0.096), (t(24) = 6.141, p<0.001). Also, at post-test blood glucose levels were higher following glucose (Mean 6.694, SEM 0.225) compared to placebo (Mean 4.403, SEM 0.091), (t(24) = 9.351, p<0.001), see Figure 5.9 below.

Table 5.15 Test Visit Blood Glucose Levels. Means and SEMs depicting the treatment x time interaction.

Treatment	Time	Mean	±	SEM
Glucose	Baseline	4.707	±	0.099
	Pre-Tasks	5.662	±	0.21
	Post-Tasks	6.694	±	0.225
Placebo	Baseline	4.662	±	0.085
	Pre-Tasks	4.49	±	0.096
	Post-Tasks	4.403	±	0.091

Figure 5.9 Test Visit Blood Glucose Levels. Pairwise comparisons for the time x treatment interaction. Figure key shows pairwise comparisons and significance levels. (**p<.001)*. Bars show standard error.**



The main effect of glucoregulation type (F(1,24) = 8.775, p = 0.007, r = 0.05) showed that overall better regulators had lower blood glucose levels (Mean 4.866, SEM 0.117) compared to poorer regulators (Mean 5.340, SEM 0.109).

5.4.2.2.1 Summary of Blood Glucose Levels and Glucoregulation Results

The oral glucose tolerance tests conducted on all participants facilitated the forming of two groups based on their incremental iAUC for blood glucose response over the OGTT, as such 'better' and

'poorer' regulators. The glucoregulation of the groups was found to be significantly different (see Figure 5.6 and Figure 5.7) with better regulators having lower levels of circulatory blood glucose levels. Analysis of blood glucose levels taken on study days confirmed that participants glucoregulation conformed to the expected differences following glucose or placebo treatments. Analysis of test visit baseline blood glucose levels found that there was a significant difference in baseline measures for the placebo visit, with poorer regulators having slightly high levels of blood glucose.

5.4.2.3 T2DM Risk Score and Glucoregulation

5.4.2.3.1 T2DM Risk Score Differences between Glucoregulation Groups

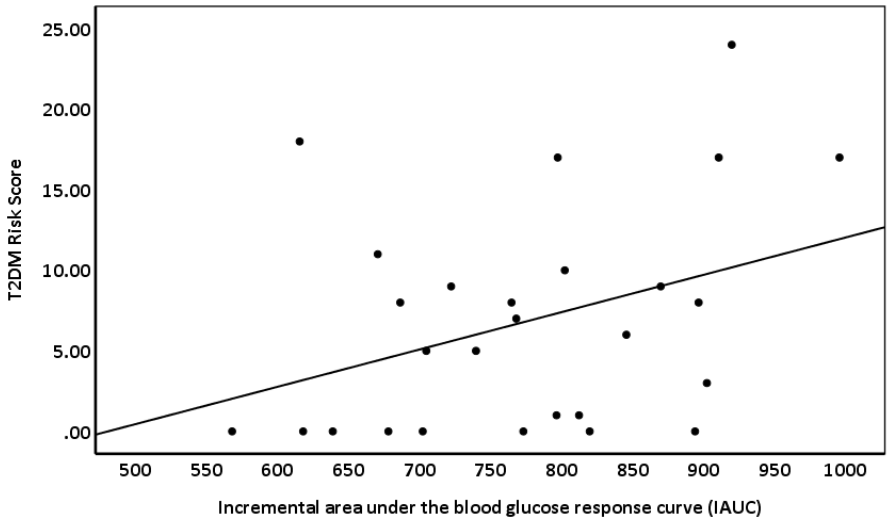
Prior to correlational analyses being conducted, a one-way ANOVA was conducted to explore whether there was a significant difference in risk scores between the two glucoregulation groups. No significant difference was found in T2DM risk scores ($F(1,25) = 0.966$, $p = .335$, $r = 0.19$) between better regulators (Mean = 5.46: SEM = 1.53) and poorer regulators (M = 8.07: SEM = 2.12).

5.4.2.3.2 T2DM Risk Score and Glucoregulation Correlational Analyses

Three sets of correlations were conducted to explore the efficiency of using a questionnaire based assessment of known T2DM risk factors alongside oral glucose tolerance testing as an indication of the potential risk of developing T2DM. Participants' iAUC measure of glucose tolerance was used in these correlational analyses as a continuous variable, rather than split groups on the basis of the median split based on iAUC.

The relationship between participants' glucoregulatory control (iAUC) and their T2DM risk score was analysed using a Pearson's product moment correlation. The analysis found a medium, positive correlation between the two variables, $r = .365$, $N = 27$, $p = 0.031$, indicating that the higher an individuals' iAUC, the higher their potential T2DM risk score. See Figure 5.10 below.

Figure 5.10 Scatterplot showing the medium positive correlation between glucoregulatory control and risk for the potential to develop T2DM.

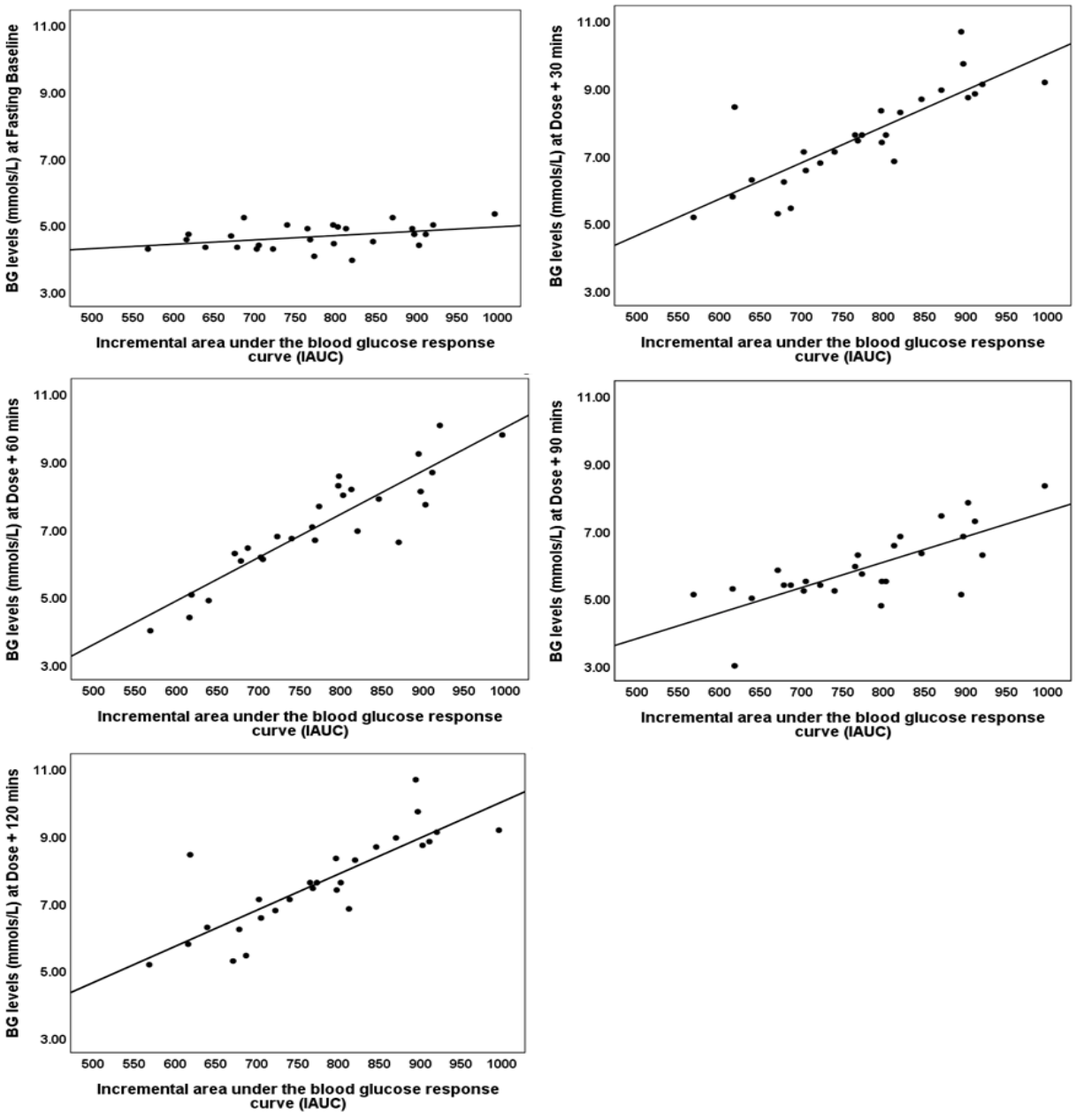


Exploring the relationship between iAUC and participants' blood glucose measures at the five time points of the OGTT a further Pearson's product moment analysis was conducted. The outcome of the correlation revealed a significant medium, positive relationship between glucoregulatory control and blood glucose levels at Fasting Baseline and Dose + 120 and a strong, positive relationship between glucoregulatory control and blood glucose levels at 30, 60 and 90 minutes post-dose. Higher blood glucose levels were related to dose response, showing post dose blood glucose levels rising as iAUC measures increased, see below for Table 5.16 and for scatterplots.

Table 5.16 iAUC Glucoregulation Measures and OGTT Response Relationship. Pearson's correlation across the five OGTT time points (p<.05;**p<.01;***p<.001)* N = 27.**

(N = 27)	iAUC	Fasting Baseline	Dose + 30 minutes	Dose + 60 minutes	Dose + 90 minutes	Dose + 120 minutes
iAUC	_	_	_	_	_	_
Fasting Baseline	.389*	_	_	_	_	_
Dose + 30 minutes	.826***	0.286	_	_	_	_
Dose + 60 minutes	.904***	.904***	.712***	_	_	_
Dose + 90 minutes	.751***	.751***	.373*	.512*	_	_
Dose + 120 minutes	.457**	0.003	0.05	0.25	.755***	_

Figure 5.11 iAUC Glucoregulation Measures and OGTT Response Relationship. Pearson's correlation scatterplots showing the relationship between iAUC measures of glucoregulation and glucose response across the five OGTT time points.



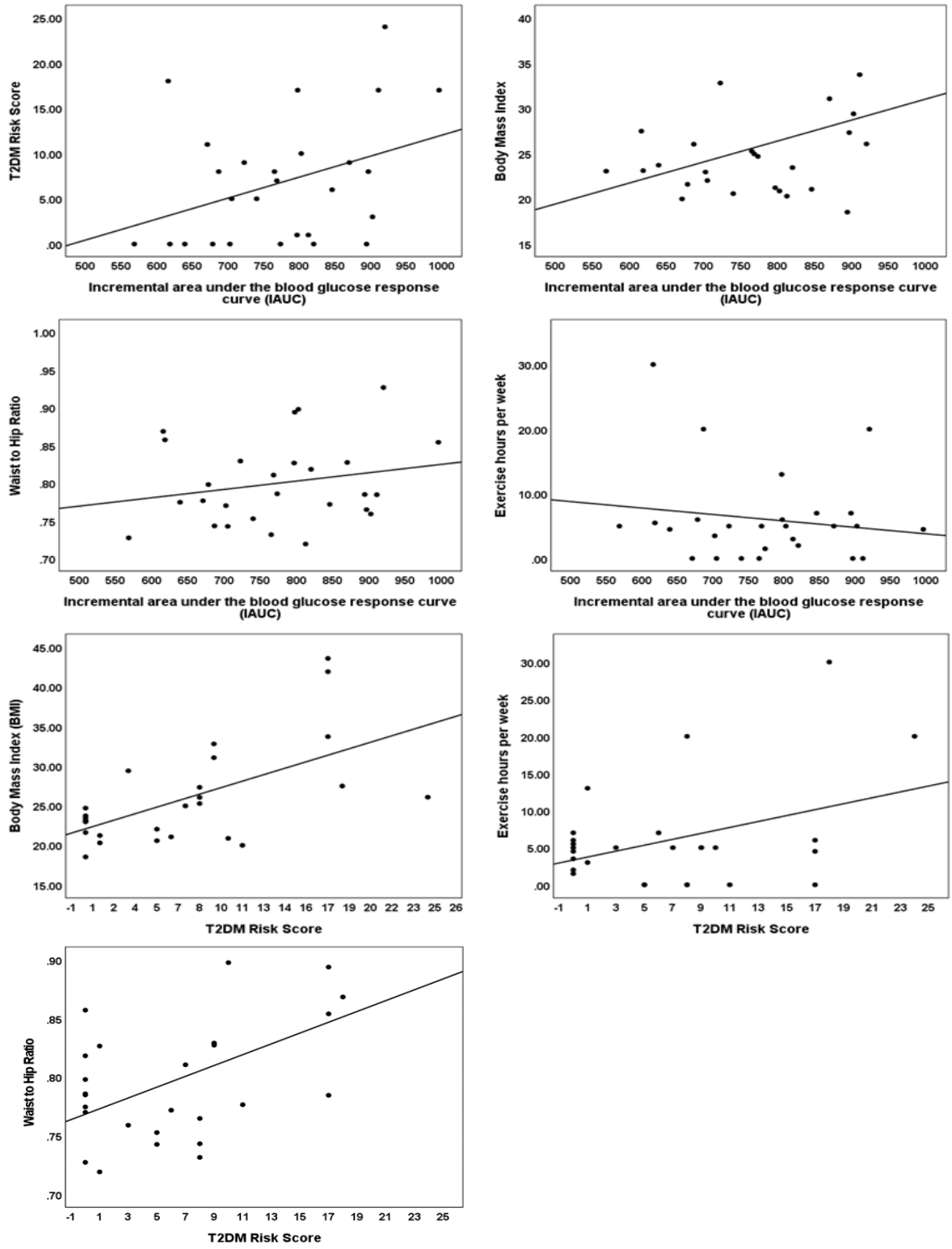
Correlational analysis conducted to explore the relationships between glucoregulatory control, body mass index (BMI), waist to hip ratio and exercise hours (self-reported) per week (see Table 5.17 below) revealed a significant medium, positive relationships between iAUC and T2DM risk scores, and iAUC and BMI. There was a medium, positive relationship between risk scores and self-reported exercise, inspection of the scatterplot shows a statistically illogical pattern. There was a strong,

positive relationship between risk scores and BMI and WHR. There was a medium, positive relationship between BMI and WHR and finally a medium, positive relationship between WHR and exercise. See Figure 5.12 for scatterplots.

Table 5.17 Risk Factor Relationships. Pearson's correlation exploring the relationship between glucoregulatory control, T2DM potential risk and BMI, WHR and Exercise (p<.05;**p<.01;***p<.001)* N = 27**

N = 27	iAUC	Risk Score	BMI	WHR	Exercise Hours
iAUC	_	_	_	_	_
Risk Score	.365*	_	_	_	_
BMI	.403*	.604***	_	_	_
WHR	0.217	.574**	.391*	_	_
Exercise Hours Per Week	-0.153	.389*	0.041	.436*	_

Figure 5.12 Risk Factor Relationships. Scatterplots from the Pearson correlation outcomes shown in table 8 above.



5.4.2.3.2.1 Summary of T2DM Risk Score and Glucoregulation Results

This analysis explored the efficiency of using a questionnaire based on known T2DM risk factors alongside glucoregulatory control measures as a means of identifying the potential risk of developing T2DM. One-way ANOVA found a non-significant difference between better and poorer glucoregulators for T2DM risk score measures. However, the outcomes of the correlational analyses provide evidence that suggests that the known associable T2DM risk factors have a significant positive relationship with blood glucose measures (iAUC) taken via an oral glucose tolerance test. As these effects have been observed in this population of healthy young adults, this positive relationship between these measures provides evidence for the efficacy of the risk score assessment model in terms of preventative interventions which may be put into place prior to the onset of T2DM.

5.4.3 Heart Rate BPM / Encoding Phase

5.4.3.1 Baseline Beats per Minute

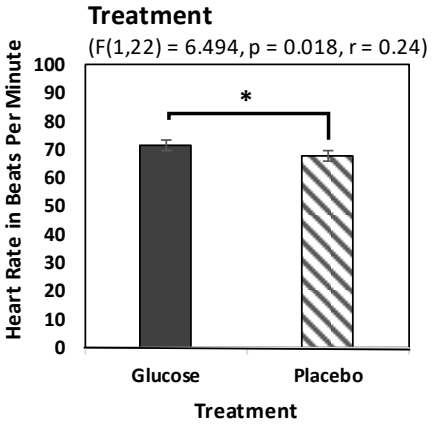
For the analysis of baseline heart rate, taken over the 60 second calibration period prior to task commencement, the primary two-way treatment x glucoregulation interaction was non-significant ($F(1,22) = 0.015$, $p = .903$, $r = 0.01$). See Table 5.18 below for analysis means and SEMs, significant main effects and interactions are shown.

Table 5.18 Baseline heart rate over 60 seconds prior to commencement of cognitive tasks. Means, SEMs and significant effects and interactions are indicated (Gluc = Glucoregulation, Tr =Treatment (*p<0.05)

Glucoregulation	N	Treatment	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	13	Glucose	70.353	±	2.247	Tr *
	13	Placebo	66.526	±	1.886	
Poorer Regulators	11	Glucose	72.476	±	2.443	
	11	Placebo	69.002	±	2.051	

The significant main effect of treatment (F(1,22) = 6.494, p = .018, r = 0.24) showed that following glucose baseline heart rate was elevated (Mean 71.42, SEM 1.66) compared to following placebo (Mean 67.764, SEM 1.39), see Figure 5.13 below.

Figure 5.13 Mean Baseline Heart Rate. Main effect of treatment. See figure key for significance levels. (p<.05)*. Bars show standard error.**



5.4.3.2 Encoding Phases Post Stimulus Heart Rate

See Appendix 5.5 for the means and SEMs for the ECG analysis of heartrate means over 0 - 1 second, 0 - 2 seconds and 0 - 3 seconds post presentation of stimuli during the encoding phase. Significant effects and interactions are indicated. The primary five-way treatment x demand x valence x time x glucoregulation ANOVA was non-significant (F(4,788) = 0.091, p = .972, r = 0.002). Significant main effects and interactions are shown in Table 5.19 below. Only significant higher order interactions are reported in the text.

Table 5.19 Encoding Phase Post Stimulus Heart Rate. ANOVA analysis of heart rate means over 0 - 1 second, 0 - 2 seconds and 0 - 3 seconds post presentation of stimuli during the encoding phase. F values, degrees of freedom, significance levels and effect sizes for interactions and main effects.

Main Effects/ Interactions	df	F	p value	r
Demand x Valence x Glucoregulation	(2,44)	3.351	0.044	0.04
Treatment	(1,22)	8.152	0.009	0.22

For the demand x valence x glucoregulation interaction ($F(2,44) = 3.351$, $p = .044$, $r = 0.04$) (see Table 5.19 above and Table 5.20 below for interaction means and SEMs), there were no effects of either glucoregulation or valence on the interaction. The interaction effect of demand showed that responses to neutral words by poorer regulators evoked elevated heart rate during high demand encoding (Mean 78.32, SEM 2.18) compared to low demand encoding (Mean 75.32, SEM 2.14), ($t(22) = 3.167$, $p = 0.004$). See Figure 5.14 below.

Figure 5.14 Encoding Phase Post Stimulus Heart Rate Pairwise comparisons from the demand x valence x glucoregulation interaction. Figure key shows pairwise comparisons and significance levels. (*p < .05). Bars show standard error.

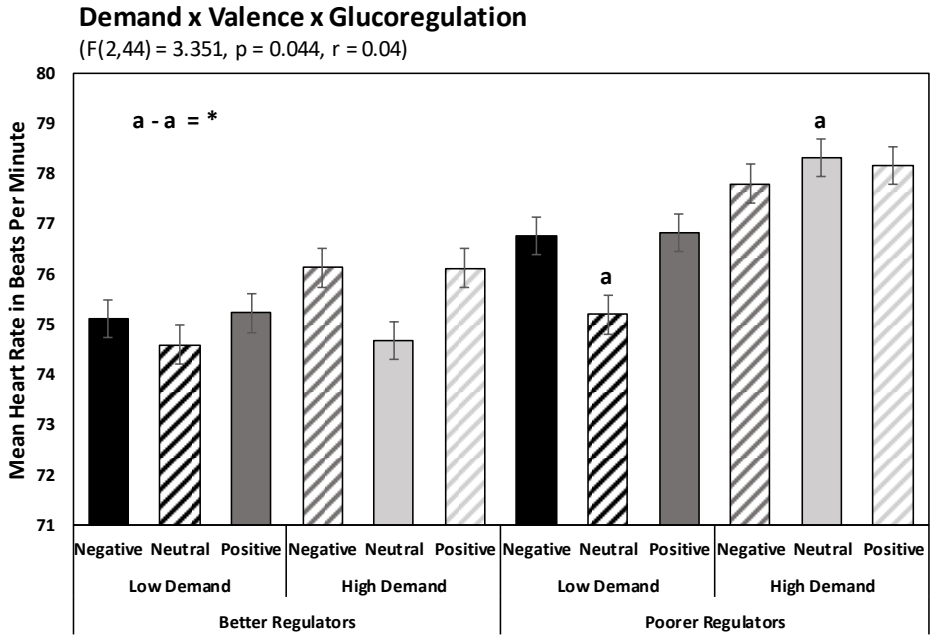
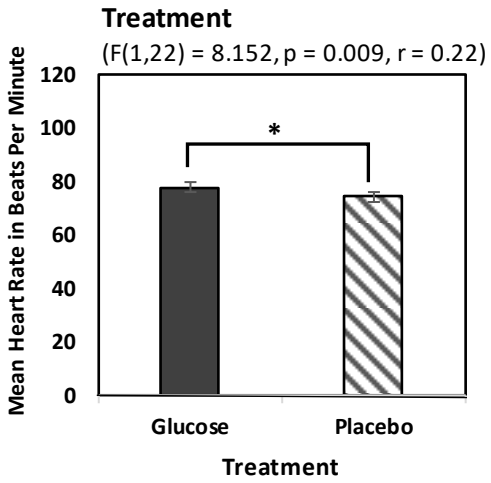


Table 5.20 Encoding Phase Post Stimulus Heart Rate. Means and SEMs depicting the demand x valence x glucoregulation interaction.

Glucoregulation	Demand	Valence	Mean	±	SEM
Better Regulators	Low Demand	Negative	75.11	±	2.164
		Neutral	74.587	±	1.97
		Positive	75.223	±	2.157
	High Demand	Negative	76.132	±	2.165
		Neutral	74.675	±	2.002
		Positive	76.116	±	2.187
Poorer Regulators	Low Demand	Negative	76.761	±	2.352
		Neutral	75.199	±	2.141
		Positive	76.828	±	2.345
	High Demand	Negative	77.799	±	2.354
		Neutral	78.324	±	2.176
		Positive	78.168	±	2.377

There was also a significant main effect of treatment (F(1,22) = 8.152, p = .009, r = 0.22) which showed elevated heart rate following glucose (Mean 78.07, SEM 1.74) compared to following placebo (Mean 74.41, SEM 1.51). See Figure 5.15 below.

Figure 5.15 Encoding Phase Post Stimulus Heart Rate. Main effect of treatment on mean heart rate (*p<0.05). Bars show standard error.



5.4.4 Heart Rate Variability

All data for HRV analyses was collected during the first phase of each session, which was a low demand timeframe.

5.4.4.1 Fasted State HRV Differences

One-way between groups ANOVA were conducted when participants were in a fasted state on time-domain and frequency-domain HRV data collected during the placebo session to assess glucoregulation differences. No significant differences were found, see Table 5.21 and

Table 5.22 below for ANOVA statistics, means and SEMs.

Table 5.21 HRV Fasted State Time-Domain Differences. Table shows one-way (glucoregulation (2) ANOVA outcomes for each of the three time-domain measures. Means, SEMs, F values, degrees of freedom, significance levels and effect sizes are shown.

	Better Regulators (N = 12)			Poorer Regulators (N = 13						
Variable	Mean	±	SEM	Mean	±	SEM	df	f	p	r
RMSSD, ms	49.76	±	6.51	61.22	±	11.05	(1,24)	0.764	0.391	0.18
SDNN, ms	70.56	±	12.20	66.87	±	9.53	(1,24)	0.058	0.812	0.05
pNN50, %	25.53	±	5.20	31.69	±	5.96	(1,24)	0.598	0.447	0.16

Table 5.22 HRV Fasted State Frequency-Domain Differences. Table shows one-way (glucoregulation (2) ANOVA outcomes for each of the four frequency-domain measures. Means, SEMs, F values, degrees of freedom, significance levels and effect sizes are shown.

	Better Regulators (N = 11)			Poorer Regulators (N = 13)						
Variable	Mean	±	SEM	Mean	±	SEM	df	f	p	r
Very Low Frequency	107.42	±	15.16	203.28	±	46.32	(1,24)	3.347	0.081	0.36
Low Frequency	142.78	±	24.27	197.68	±	54.35	(1,24)	0.752	0.395	0.18
High Frequency	148.16	±	37.67	261.54	±	98.43	(1,24)	1.011	0.326	0.21
LF/HF	1.60	±	0.42	1.41	±	0.44	(1,24)	0.094	0.762	0.06

5.4.4.2 Time-Domain Metrics

5.4.4.2.1 RMSSD

For the analysis of the HRV measure of RMSSD in milliseconds, taken over 10 minutes from task phase commencement, the primary two-way treatment x glucoregulation interaction was non-significant ($F(1,20) = 0.803$, $p = .381$, $r = 0.07$). See Table 5.23 below for analysis means and SEMs, there were no significant main effects or interactions.

Table 5.23 HRV Analysis of RMSSD. Means, SEMs in milliseconds over 10 minutes from commencement of task phase via the two-way mixed factorial treatment x glucoregulation ANOVA. There were no significant main effects or interactions.

Glucoregulation	N	Treatment	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	11	Glucose	57.79	±	7.709	–
	11	Placebo	51.192	±	10.444	
Poorer Regulators	11	Glucose	59.559	±	7.709	
	11	Placebo	61.467	±	10.444	

5.4.4.2.2 SDNN

For the analysis of the HRV measure of SDNN in milliseconds, taken over 10 minutes from task phase commencement, the primary two-way treatment x glucoregulation interaction was non-significant ($F(1,20) = 0.192$, $p = .666$, $r = 0.04$). See Table 5.24 below for analysis means and SEMs, there were no significant main effects or interactions.

Table 5.24 HRV Analysis of SDNN. Means, SEMs in milliseconds over 10 minutes from commencement of task phase via the two-way mixed factorial treatment x glucoregulation ANOVA. There were no significant main effects or interactions.

Glucoregulation	N	Treatment	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	11	Glucose	72.075	±	7.454	-
	11	Placebo	73.369	±	12.179	
Poorer Regulators	11	Glucose	71.155	±	7.454	
	11	Placebo	67.365	±	12.179	

5.4.4.2.3 pNN50

For the analysis of the HRV measure of pNN50 as a percentage of the number of 5 minute RR intervals differing by more than 50%, taken over 10 minutes from task phase commencement, the primary two-way treatment x glucoregulation interaction was non-significant ($F(1,20) = 0.180$, $p = .676$, $r = 0.47$). See Table 5.25 below for analysis means and SEMs, there were no significant main effects or interactions.

Table 5.25 HRV Analysis of pNN50. Means, SEMs in milliseconds over 10 minutes from commencement of task phase via the two-way mixed factorial treatment x glucoregulation ANOVA. There were no significant main effects or interactions.

Glucoregulation	N	Treatment	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	11	Glucose	33.582	±	5.262	-
	11	Placebo	26.735	±	6.174	
Poorer Regulators	11	Glucose	33.244	±	5.262	
	11	Placebo	29.708	±	6.174	

5.4.4.3 Frequency Domain Metrics

5.4.4.3.1 Very Low Frequency Band

For the analysis of the power in the VLF frequency band in ms^2, taken over 10 minutes from task phase commencement, the primary two-way treatment x glucoregulation interaction was non-significant ($F(1,19) = 2.556$, $p = .126$, $r = 0.16$). See Table 5.26 below for analysis means and SEMs, there were no significant main effects or interactions.

Table 5.26 HRV Analysis of VLF Band. Means, SEMs in ms^2 over 10 minutes from commencement of task phase via the two-way mixed factorial treatment x glucoregulation ANOVA. There were no significant main effects or interactions.

Glucoregulation	N	Treatment	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	10	Glucose	146.441	±	41.855	–
	10	Placebo	110.195	±	42.294	
Poorer Regulators	11	Glucose	171.186	±	39.907	
	11	Placebo	219.559	±	40.325	

5.4.4.3.2 Low Frequency Band

For the analysis of the power in the LF frequency band in ms^2, taken over 10 minutes from task phase commencement, the primary two-way treatment x glucoregulation interaction was non-significant ($F(1,19) = 3.070$, $p = .096$, $r = 0.14$). See Table 5.27 below for analysis means and SEMs, there were no significant main effects or interactions.

Table 5.27 HRV Analysis of LF Band. Means, SEMs in ms^2 over 10 minutes from commencement of task phase via the two-way mixed factorial treatment x glucoregulation ANOVA. There were no significant main effects or interactions.

Glucoregulation	N	Treatment	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	10	Glucose	179.583	±	46.961	–
	10	Placebo	143.508	±	51.057	
Poorer Regulators	11	Glucose	171.781	±	44.776	
	11	Placebo	218.241	±	48.681	

5.4.4.3.3 High Frequency Band

For the analysis of the power in the HF frequency band in ms^2, taken over 10 minutes from task phase commencement, the primary two-way treatment x glucoregulation interaction was non-significant ($F(1,19) = 0.815$, $p = .378$, $r = 0.07$). See Table 5.28 below for analysis means and SEMs, there were no significant main effects or interactions.

Table 5.28 HRV Analysis of HF Band. Means, SEMs in ms^2 over 10 minutes from commencement of task phase via the two-way mixed factorial treatment x glucoregulation ANOVA. There were no significant main effects or interactions.

Glucoregulation	N	Treatment	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	10	Glucose	172.323	±	56.941	-
	10	Placebo	157.297	±	92.809	
Poorer Regulators	11	Glucose	222.025	±	54.291	
	11	Placebo	277.758	±	88.49	

5.4.4.3.4 Sympathetic-Vagal Balance (LF/HF)

For the analysis of the HRV measure of sympathetic-vagal balance, taken over 10 minutes from task phase commencement, the primary two-way treatment x glucoregulation interaction was non-significant ($F(1,20) = 0.181$, $p = 0.675$, $r = 0.06$). See Table 5.29 below for analysis means and SEMs, there were no significant main effects or interactions.

Table 5.29 HRV Analysis of LF/HF Band. Means, SEMs over 10 minutes from commencement of task phase via the two-way mixed factorial treatment x glucoregulation ANOVA. There were no significant main effects or interactions.

Glucoregulation	N	Treatment	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	11	Glucose	1.179	±	0.169	-
	11	Placebo	1.529	±	0.483	
Poorer Regulators	11	Glucose	0.961	±	0.169	
	11	Placebo	1.576	±	0.483	

5.4.4.4 HRV Correlational Analysis

Pearson's product moment correlations were conducted to explore relationships between the four participant measures of glucoregulatory control (iAUC), fasting blood glucose levels, T2DM risk scores and baseline heart rate (in BPM), and the time-domain and frequency domain metrics of HRV. See below in Table 5.30, significant correlations are highlighted in red.

This chapter investigated whether poorer measures of these four participant characteristics would correlate with lower levels of heart rate variability. For better regulators (see Table 5.30 (a) below) there was a limited number of significant correlations between iAUC and HRV metrics, following glucose there were significant large negative correlations between iAUC and the HRV metrics VLF and LF with higher iAUC correlating to lower HRV. Also, for better regulators, following placebo there was a significant large negative correlation between iAUC and sympathetic-vagal balance (LF/HF), again higher iAUC correlating with lower sympathetic-vagal balance.

For poorer glucoregulators and following glucose (see Table 5.30 (b) below) significant large negative correlations were more global. Higher iAUC related to lower RMSSD, SDNN, LF and HF. As fasting blood glucose levels elevated, RMSDD, SDNN, pNN50 and high frequency power were all lower. As fasting blood glucose levels increased RMSSD, SDNN,pNN50 and high frequency power were all lower.

Elevated T2DM risk scores were associated with lower RMSSD, SDNN, pNN50, VLF, LF and HF. Higher heart rate in beats per minute was also associated with lower SDNN, pNN50 and LF.

For poorer glucoregulators following placebo (see Table 5.30 (b)) there were medium negative correlations between iAUC and SDNN, VLF and LF, all of which diminished as iAUC increased. There were medium negative correlations between fasting blood glucose levels and RMSSD and HF showing elevated blood glucose correlating with lower RMSSD and HF. T2DM risk scores showed large negative correlations with SDNN, VLF and LF, all of which were lower as risk increased.

Table 5.30 Pearson's product moment correlation outcomes for (a) better glucoregulators following glucose and placebo and (b) poorer glucoregulators following glucose and placebo, 'r' values and 'p' values are shown. Significant relationships are emboldened in red.

(a) Better Regulators		Better Glucoregulators Following Glucose								Better Glucoregulators Following Placebo						
Participant Measures	r / p	RMSSD	SDNN	pNN50	VLF	LF	HF	LF/HF	r / p	RMSSD	SDNN	pNN50	VLF	LF	HF	LF/HF
AUC	r	-0.519	-0.478	-0.347	-.605*	-.567*	-0.477	0.245	r	-0.091	-0.161	-0.013	-0.365	-0.169	0.060	-0.531
	p	0.051	0.068	0.148	0.024	0.034	0.069	0.234	p	0.389	0.308	0.484	0.135	0.309	0.431	0.038
Fasting Blood Glucose Levels	r	0.031	0.020	0.108	-0.318	-0.104	-0.010	-0.235	r	0.195	0.127	0.161	-0.244	0.170	0.201	-0.365
	p	0.464	0.476	0.376	0.170	0.381	0.489	0.243	p	0.272	0.347	0.308	0.235	0.308	0.277	0.122
T2DM Risk Score	r	0.033	0.011	-0.058	-0.281	0.096	0.010	0.279	r	0.470	0.328	0.310	-0.361	0.103	0.447	-0.369
	p	0.462	0.488	0.433	0.202	0.389	0.489	0.203	p	0.062	0.149	0.164	0.138	0.381	0.084	0.119
Baseline Heart Rate in Beats per Minute	r	0.004	0.267	-0.239	0.386	0.359	0.234	0.467	r	-0.124	-0.033	-0.221	-0.273	-0.136	-0.152	-0.019
	p	0.495	0.213	0.239	0.120	0.139	0.244	0.074	p	0.351	0.460	0.245	0.208	0.345	0.328	0.477
(b) Poorer Regulators		**Poorer Glucoregulators Following Glucose**								**Poorer Glucoregulators Following Placebo**						
Participant Measures	r / p	RMSSD	SDNN	pNN50	VLF	LF	HF	LF/HF	r / p	RMSSD	SDNN	pNN50	VLF	LF	HF	LF/HF
AUC	r	-.537*	-.642*	-0.453	-0.496	-.547*	-0.512	-0.138	r	-0.355	-0.492	-0.206	-0.518	-0.520	-0.398	-0.137
	p	0.044	0.017	0.081	0.060	0.041	0.054	0.342	p	0.117	0.044	0.250	0.035	0.034	0.089	0.328
Fasting Blood Glucose Levels	r	-.721**	-0.518	-.700**	-0.130	-0.147	-.742**	0.502	r	-0.478	-0.332	-0.380	-0.224	-0.236	-0.499	0.104
	p	0.006	0.051	0.008	0.352	0.333	0.004	0.058	p	0.049	0.134	0.100	0.231	0.219	0.041	0.367
T2DM Risk Score	r	-.615*	-.761**	-.662*	-.523*	-.576*	-.593*	-0.078	r	-0.276	-0.513	-0.040	-0.523	-0.579	-0.336	-0.307
	p	0.022	0.003	0.013	0.049	0.032	0.027	0.410	p	0.181	0.036	0.448	0.033	0.019	0.131	0.154
Baseline Heart Rate in Beats per Minute	r	-0.519	-.612*	-.679*	-0.183	-.628*	-0.405	-0.087	r	-0.049	-0.276	-0.110	-0.183	-0.342	0.032	-0.445
	p	0.051	0.023	0.011	0.295	0.019	0.108	0.400	p	0.443	0.206	0.374	0.295	0.152	0.463	0.085

5.4.4.4.1 Summary of Heart Rate and HRV analysis Results

See Sections 5.4.2.3.2.1 and 5.4.4

Glucose treatment was seen to elevate the 60 second pre-test heart rate beats per minute and during the encoding phase. Poorer regulators had elevated heart rate in response to neutral words during the high demand encoding phase. The analyses of difference (ANOVAs) of heart rate variability did not reveal any significant main effects or interactions for time-domain measures of RMSSD, SDSD, pNN50 or the four frequency-domain measures of very low frequency, low frequency, high frequency, or sympathetic-vagal balance (LF/HF). However, for future relevance, whilst the differences in HRV measure between glucoregulation groups were non-significant, inspection of the means indicated that better regulators had enhanced HRV compared to poorer regulators (see section 5.4.4 for all measures). Analyses of relationships (Pearson's correlations) did show significant correlations between measures of pNN50 with both T2DM risk scores and baseline heart rate in beats per minute. Here, pNN50 measures are seen to get higher as BPM and risk get lower.

5.5 Behavioural Results

5.5.1 Mood, and Physical and Mental State Measures

See Table 5.31 below for means and SEMs of the three-way ANOVA, significant effects are indicated.

Table 5.31 Mood, and Physical and Mental State Measures. Means, SEMs for better and poorer glucoregulators. Means, SEMs and significant effects are indicated (Tr = Treatment; *Gluc = Glucoregulation Group, Ti = Time, (*p<.05*p<0.005,*)**

Outcome	Timepoint	Glucoregulation	N=	Glucose			Placebo			Significant Effects and Interactions
				Means	±	SEM	Means	±	SEM	
Alert	Baseline	Better	13	51.08	±	4.82	55.04	±	5.02	-
		Poorer	13	58.91	±	3.37	56.87	±	3.86	
	Post-Tasks	Better	13	56.03	±	5.03	52.57	±	5.84	
		Poorer	13	62.64	±	4.13	61.71	±	4.34	
Content	Baseline	Better	13	56.80	±	6.25	59.58	±	4.60	-
		Poorer	13	64.26	±	3.27	66.04	±	2.13	
	Post-Tasks	Better	13	56.73	±	6.35	59.45	±	4.75	
		Poorer	13	64.98	±	3.95	65.92	±	3.64	
Calm	Baseline	Better	13	52.64	±	3.73	52.64	±	3.31	-
		Poorer	13	62.65	±	3.32	68.55	±	3.21	
	Post-Tasks	Better	13	52.68	±	3.92	47.82	±	2.11	
		Poorer	13	57.75	±	2.96	61.55	±	2.94	
Mental Energy	Baseline	Better	13	52.00	±	5.69	48.55	±	3.37	Ti xTr x Gluc*
		Poorer	13	54.60	±	3.94	56.30	±	3.50	
	Post-Tasks	Better	13	56.45	±	4.19	57.27	±	5.32	
		Poorer	13	53.00	±	4.42	56.50	±	4.93	
Concentration	Baseline	Better	13	58.27	±	2.81	64.00	±	4.05	-
		Poorer	13	58.30	±	4.69	56.80	±	5.45	
	Post-Tasks	Better	13	61.36	±	6.15	54.91	±	6.12	
		Poorer	13	54.40	±	7.04	54.10	±	7.13	
Fullness	Baseline	Better	13	34.36	±	5.81	31.82	±	5.65	Ti xTr **
		Poorer	13	29.70	±	5.59	26.70	±	3.02	
	Post-Tasks	Better	13	36.55	±	5.04	36.73	±	3.88	
		Poorer	13	41.90	±	5.52	31.60	±	6.68	
Physical Stamina	Baseline	Better	13	45.91	±	6.18	47.73	±	4.53	-
		Poorer	13	53.70	±	6.14	49.10	±	6.67	
	Post-Tasks	Better	13	49.09	±	6.45	53.09	±	5.91	
		Poorer	13	47.10	±	6.42	50.80	±	5.63	
Mental Fatigue	Baseline	Better	13	46.27	±	6.08	51.55	±	4.39	-
		Poorer	13	44.90	±	7.02	51.20	±	5.41	
	Post-Tasks	Better	13	44.45	±	6.25	49.27	±	6.85	
		Poorer	13	46.80	±	4.65	51.00	±	6.44	
Hunger	Baseline	Better	13	61.09	±	6.74	64.45	±	4.77	-
		Poorer	13	67.00	±	5.43	68.50	±	5.25	
	Post-Tasks	Better	13	68.36	±	5.47	62.09	±	7.46	
		Poorer	13	65.90	±	5.32	72.40	±	4.68	
Mental Stamina	Baseline	Better	13	52.27	±	5.23	52.82	±	3.84	Tr *
		Poorer	13	52.80	±	5.63	47.60	±	4.87	
	Post-Tasks	Better	13	51.82	±	5.97	51.18	±	5.58	
		Poorer	13	48.10	±	3.87	54.20	±	5.04	
Physically Tired	Baseline	Better	13	49.00	±	5.56	49.27	±	5.98	-
		Poorer	13	54.20	±	7.72	64.10	±	3.85	
	Post-Tasks	Better	13	49.55	±	7.00	53.45	±	7.94	
		Poorer	13	50.70	±	5.47	47.50	±	6.22	
Thirst	Baseline	Better	13	49.91	±	7.26	53.18	±	5.77	-
		Poorer	13	58.90	±	7.30	52.67	±	8.15	
	Post-Tasks	Better	13	45.09	±	7.55	55.36	±	5.04	
		Poorer	13	54.30	±	9.04	60.80	±	6.79	
Mentally Tired	Baseline	Better	13	49.82	±	3.88	48.27	±	2.88	-
		Poorer	13	49.80	±	9.18	39.89	±	6.04	
	Post-Tasks	Better	13	51.73	±	5.25	48.18	±	3.77	
		Poorer	13	47.40	±	7.88	53.40	±	4.22	

Three-way mixed factorial (Glucoregulation (2) x Treatment (2) x Time (2)) ANOVAs were conducted on each of the subjective measures of 'alertness', 'contentedness', 'calmness', 'mental energy', 'concentration', 'fullness', 'physical stamina', 'mental fatigue', 'hunger', 'mental stamina', 'physical tiredness', 'thirst' and 'mental tiredness'. None of the primary three-way interactions were found to be significant, see Table 5.32 below for statistical justifications.

Table 5.32 Mood, and Physical and Mental State ANOVAS. F values, degrees of freedom, significance levels and effect sizes are indicated.

Physical and Mental States	df	F	p value	r
Alertness	(1,24)	0.088	0.770	0.02
Contentedness	(1,24)	0.607	0.443	0.05
Calmness	(1,24)	0.275	0.605	0.03
Mental Energy	**(1,24)**	**6.041**	**0.022**	**0.16**
Concentration	(1,24)	2.476	0.129	0.14
Fullness	(1,24)	0.047	0.830	0.01
Physical Stamina	(1,24)	0.117	0.736	0.02
Mental Fatigue	(1,24)	0.533	0.102	0.15
Hunger	(1,24)	3.565	0.071	0.15
Mental Stamina	(1,24)	0.121	0.731	0.02
Physical Tiredness	(1,24)	0.133	0.718	0.03
Thirst	(1,24)	1.457	0.239	0.08
Mental Tiredness	(1,24)	0.180	0.675	0.04

Main effects and interactions involving treatment and/or glucoregulation for physical and mental state assessments, with outcomes of significant post hoc pairwise comparisons, are reported below.

The analysis of mental energy revealed a time x treatment x glucoregulation interaction ($F(1,24) = 6.041$, $p = .022$, $r = 0.16$) (see Table 5.32 above) showing that following glucose better regulators had higher levels of mental energy at post-test (Mean 6.354, SEM 0.423) compared to baseline (Mean 5.300, SEM 0.402), ($t(24) = 2.291$, $p = 0.031$), see Figure 5.16 below.

Figure 5.16 Mental Energy. Time x Treatment x Glucoregulation interactions, pairwise comparison showing that following glucose better regulators had more self-reported mental energy than at baseline. (p < .05).* Bars show standard error.**

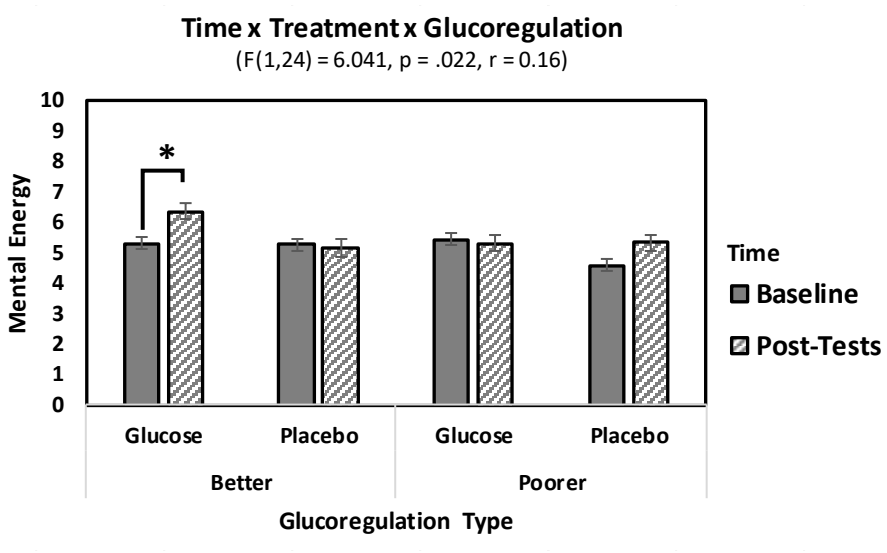
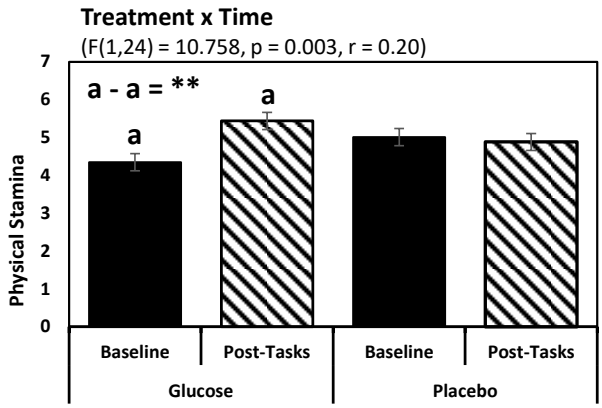


Figure 5.17 Physical Stamina. Treatment x Time Interaction. Pairwise comparison showing that following glucose, participants reported greater physical stamina at post-tasks than at baseline. (*p < .005).* Bars show standard error.**



For physical stamina, the treatment x time interaction (F(1,24) = 10.758, p=.003, r = 0.20) showed that participants reported greater levels of physical stamina following glucose at post-test (Mean 5.440, SEM 0.310) compared to baseline (Mean 4.348, SEM 0.283), (t(24) = 3.792, p = .001).

For mental stamina, there was a main effect of treatment with higher levels of mental stamina ($F(1,24) = 8.816$, $p = 0.007$, $r = 0.19$) seen for the glucose condition (Mean 5.548, SEM 0.241) compared to the placebo condition (Mean 4.959, SEM 0.228).

5.5.1.1 Summary of Physical and Mental State Measures Results

Mental energy showed an interaction between time, treatment and glucoregulation, following glucose better regulators had more mental energy post-test relative to baseline.

Physical stamina analysis revealed an interaction between treatment and time showing that following glucose participants felt that they had more physical stamina at post-test in comparison to baseline.

Mental stamina analysis showed a main effect of treatment with more mental stamina following glucose compared to placebo.

5.5.2 Sustained Attention to Response Task (SART)

5.5.2.1 SART Accuracy

See Table 5.33 below for means and SEMs, significant effects are indicated.

Table 5.33 Sustained Attention to Response Task Accuracy. Means, SEMs for the three-way mixed factorial treatment x SART x glucoregulation ANOVA. Significant effects and interactions are indicated (Gluc = Glucoregulation, Tr =Treatment, SART = SART (*p<0.05)

Glucoregulation	N	Treatment	SART	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	11	Glucose	Go	64.935	±	5.708	
	11		NoGo	41.819	±	6.851	
	11	Placebo	Go	64.318	±	5.787	
	11		NoGo	40.26	±	6.687	Gluc *
Poorer Regulators	12	Glucose	Go	53.839	±	5.465	
	12		NoGo	62.381	±	6.559	Gluc x SART*
	12	Placebo	Go	49.674	±	5.54	
	12		NoGo	62.142	±	6.402	

The analysis of SART accuracy data showed that the primary three-way treatment x SART responses x glucoregulation interaction was non-significant (F(1,21) = 0.183, p = .674, r = 0.03). See Table 5.34 below for significant main effects and interactions.

Table 5.34 Sustained attention to response task (SART) accuracy ANOVA. F values, degrees of freedom, significance levels and effect sizes for interactions and main effects are shown.

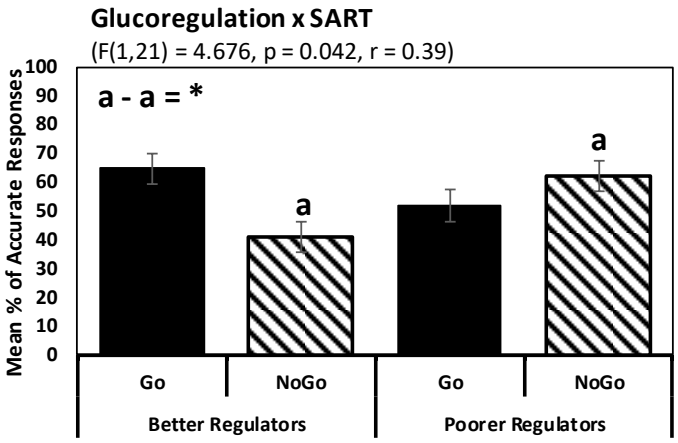
Main Effects/ Interactions	Df	F	p value	r
Glucoregulation x SART	(1,21)	4.676	0.042	0.39
Glucoregulation	(1,21)	5.586	0.028	0.09

There was a glucoregulation x SART interaction (F(1,21) = 4.676, p = .042, r = 0.39), (see Table 5.34 above and Table 5.35 below for interaction means and SEMs). Significant pairwise comparisons revealed that effects of glucoregulation on the interaction showed poorer regulators as having a higher percentage of accurate NoGo SART responses compared to better regulators, see Figure 5.18 below. The type of SART response had no effect on the interaction.

Table 5.35 Sustained Attention to Response Task Accuracy. Means and SEMs depicting the glucoregulation x SART interaction.

Glucoregulation	SART	Mean	±	SEM
Better Regulators	Go	64.627	±	5.438
	NoGo	41.04	±	6.207
Poorer Regulators	Go	51.757	±	5.206
	NoGo	62.261	±	5.943

Figure 5.18 Sustained Attention to Response Task Accuracy. Pairwise comparisons from the glucoregulation x SART interaction. Figure key shows pairwise comparison and significance level. (*p < .05). Bars show standard error.



5.5.2.2 SART Response Reaction Time

See Table 5.36 below for the means and SEMs for the SART response time analysis. Significant effects and interactions are indicated.

Table 5.36 Sustained Attention to Response Task Response Time. Means and SEMs in (milliseconds) for the two-way mixed factorial treatment x glucoregulation ANOVA. Significant effects and interactions are indicated (Gluc = Glucoregulation, Tr =Treatment, SART = SART (*p<0.05).

Glucoregulation	N	Treatment	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	11	Glucose	167.637	±	9.565	Gluc *
	11	Placebo	158.914	±	15.167	
Poorer Regulators	12	Glucose	188.09	±	9.158	
	12	Placebo	207.374	±	14.522	

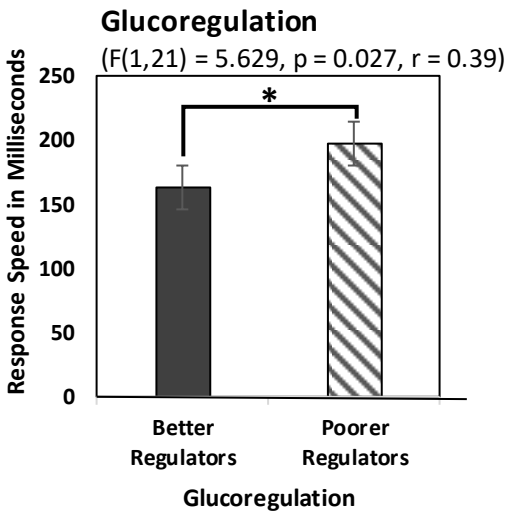
The analysis of SART response time data showed that the primary two-way treatment x glucoregulation interaction was non-significant (F(1,21) = 2.017, p = .170, r = 0.16). Significant main effects and interactions are shown in Table 5.37 below.

Table 5.37 Sustained Attention to Response Task Response Time ANOVA. F values, degrees of freedom, significance levels and effect sizes for interactions and main effects are shown.

Main Effects/ Interactions	Df	F	p value	r
Glucoregulation	(1,21)	5.629	0.027	0.39

The main effect of glucoregulation (F(1,21) = 5.629, p = .027, r = 0.39) (see Table 5.37 above) revealed that better glucoregulators had faster response times, in milliseconds (Mean 163.28, SEM 10.49) compared to poorer regulators (Mean 197.73, SEM 10.04), see Figure 5.19 below.

Figure 5.19 Sustained Attention to Response Task Response Time
Pairwise comparison from the main effect of glucoregulation.
See figure key for significance levels (*p < .05). Bars show standard error.



5.5.2.2.1 Summary of Sustained Attention to Task (SART) Results

Poorer regulators were seen to make more accurate NoGo SART responses than did better regulators whereas in terms of response times, faster responses were made by better glucoregulators. Speculatively this may be because the faster responses by better glucoregulators allowed them to register more incorrect NoGo responses, whereas for poorer regulators their slower responses breached the 250 millisecond time-out and as such registering correct NoGo responses.

5.5.3 Word Recognition Behavioural Results

5.5.3.1 Word Recognition Old/New Words Accuracy

See Appendix 5.6 the means and SEM for the behavioural data for the Word Recognition Accuracy analysis. Significant effects and interactions are indicated.

The primary five-way treatment x demand x word type x valence x glucoregulation interaction was not significant (F(2,48) = 1.275, p = .289, r = 0.03). Significant main effects and interactions are shown in Table 5.38 below. Only significant higher order interactions are reported in the text.

Table 5.38 Word Recognition Old/New Accuracy ANOVA. F values, degrees of freedom, significance levels and effect sizes for interactions and main effects are indicated.

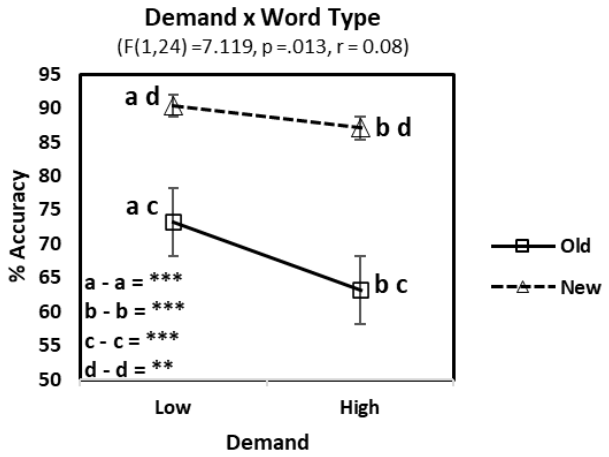
Main Effects/ Interactions	Df	F	p value	r
Demand x Word Type	(1,24)	7.119	0.013	0.08
Glucoregulation	(1,24)	6.97	0.014	0.19
Demand	(1,24)	34.879	<0.001	0.17
Word Type	(1,24)	25.875	<0.001	0.51
Valence	(2,48)	8.886	0.001	0.09

The demand x word type interaction (F(1,24) = 7.119, p = .013, r = 0.08) (see Table 5.38 above) showed a similar pattern following both low demand encoding (no mouse tracking task during the encoding of words) and high demand (tracking during encoding) conditions. Significant pairwise comparisons can be seen in Table 5.39 below. Demand comparisons revealed that following low demand encoding accuracy was greater for correctly rejected 'new' words relative to correctly recognised 'old' words. High demand encoding also resulted in greater accuracy for new words compared to old words. Word Type comparisons revealed that accuracy was greater for old words following low demand than following high demand and similarly new word accuracy was greater following low demand see Figure 5.20 below.

Table 5.39 Word Recognition Old/New Accuracy. Significant pairwise comparisons for the two-way demand x word type interaction. Group, pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

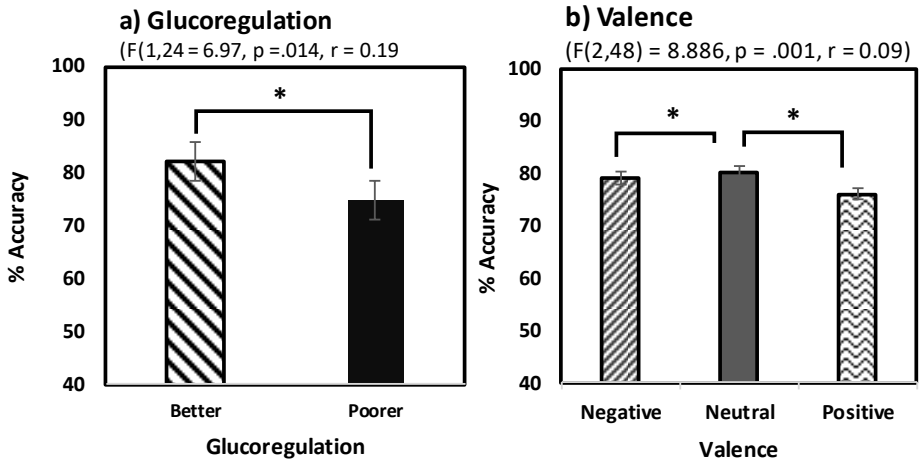
Condition	Pairwise Differences in Accuracy	Mean(SEM)	t(24)=	p Value
Low Demand	New Words > Old Words	Old Words (Mean 73.25, SEM 2.76)	4.780	<0.001
		New Words (Mean 90.36, SEM 1.61)		
High Demand	New Words > Old Words	Old Words (Mean 63.21, SEM 3.52)	4.996	<0.001
		New Words (Mean 87.04, SEM 2.092)		
Old Words	Low Demand > High Demand	Low Demand (Mean 73.25, SEM 2.76)	4.569	<0.001
		High Demand (Mean 63.21, SEM 3.52)		
New Words	Low Demand > High Demand	Low Demand (Mean 90.36, SEM 1.61)	3.484	0.002
		High Demand (Mean 87.04, SEM 2.09)		

Figure 5.20 Word Recognition Old/New Accuracy. Demand x Word Type interaction showing accuracy as a percentage for old and new recognitions following high demand and low demand encoding Figure key shows pairwise comparisons and significance levels. (p<.005,*** p<.001). Bars show standard error.**



The main effect of glucoregulation (F(1,24) = 6.97, p = .014, r = 0.19) revealed that better regulators made more accurate recognitions (Mean 82.176, SEM 2.063) than poorer regulators (Mean 74.752, SEM 1.910), see Figure 5.21a below. The main effect of valence revealed greater accuracy for neutral words (Mean 80.213, SEM 1.440) compared to negative words (Mean 79.058, SEM 1.582), (t(23) =2.877, p = .025) and compared to positive words (Mean 76.121, SEM 1.535), (t(23) =5.027, p < .001) see Figure 5.21b below.

Figure 5.21 Word Recognition Old/New Accuracy Significant Main effects of the treatment x demand x word type x valence x glucoregulation ANOVA showing accuracy as a percentage. Figure key shows pairwise comparisons and significance levels. (*p<.05). Bars show standard error.



5.5.3.2 Word Recognition Old/New Response Reaction Time

See Table 5.40 below for the means and SEMs for the behavioural data for the word recognition response RT analysis. Significant effects and interactions are indicated.

Table 5.40 Word Recognition Old/New Response Reaction Time. Means, SEMs for the outcomes the five-way mixed factorial treatment x demand x word type x valence x glucoregulation ANOVA. Significant effects and interactions are indicated (Gluc = Glucoregulation, Tr =Treatment, Dem = Demand, WdTyp = Word Type, Val = Valence) (*p<0.05, ***p<0.001)

Outcome	Gluco-regulation	Treatment	Demand	Word Type	N	Valence	Mean	±	SEM	Significant Effects and Interactions
Response Reaction Time in Milliseconds	Better Regulators	Glucose	Low Demand Encoding	Old Word	12	Negative	820.30	±	70.48	
					12	Neutral	980.68	±	106.04	
					12	Positive	838.90	±	61.86	
				New Word	12	Negative	907.13	±	69.13	
					12	Neutral	923.43	±	92.13	
					12	Positive	891.07	±	77.96	
			High Demand Encoding	Old Word	12	Negative	872.51	±	51.26	
					12	Neutral	923.49	±	79.43	
					12	Positive	963.66	±	65.04	
				New Word	12	Negative	826.38	±	66.77	
					12	Neutral	818.90	±	66.70	
					12	Positive	835.03	±	65.53	
		Placebo	Low Demand Encoding	Old Word	12	Negative	860.49	±	79.74	
					12	Neutral	956.56	±	91.55	
					12	Positive	785.66	±	58.56	
				New Word	12	Negative	811.52	±	65.97	
					12	Neutral	902.46	±	72.27	Tr x Dem x WdTyp x Val x Gluc*
					12	Positive	786.99	±	61.19	
			High Demand Encoding	Old Word	12	Negative	894.56	±	85.17	
					12	Neutral	956.64	±	65.83	Dem x WdTyp x Gluc*
					12	Positive	1015.19	±	82.36	
				New Word	12	Negative	834.27	±	64.16	Dem x Gluc*
					12	Neutral	850.10	±	67.71	
					12	Positive	875.95	±	72.80	Dem x Val***
	Poorer Regulators	Glucose	Low Demand Encoding	Old Word	14	Negative	1016.82	±	65.25	
					14	Neutral	1190.18	±	98.17	WdTyp x Val*
					14	Positive	981.69	±	57.27	
				New Word	14	Negative	896.87	±	64.00	WdTyp *
					14	Neutral	1002.44	±	85.30	
					14	Positive	984.12	±	72.17	Valence *
			High Demand Encoding	Old Word	14	Negative	931.08	±	47.46	
					14	Neutral	1027.23	±	73.54	
					14	Positive	995.94	±	60.21	
				New Word	14	Negative	991.28	±	61.81	
					14	Neutral	907.87	±	61.75	
					14	Positive	884.29	±	60.67	
		Placebo	Low Demand Encoding	Old Word	14	Negative	1013.83	±	73.82	
					14	Neutral	1172.69	±	84.76	
					14	Positive	1065.90	±	54.22	
				New Word	14	Negative	997.19	±	61.08	
					14	Neutral	1018.37	±	66.91	
					14	Positive	918.75	±	56.65	
			High Demand Encoding	Old Word	14	Negative	1036.79	±	78.85	
					14	Neutral	1028.20	±	60.95	
					14	Positive	983.01	±	76.25	
				New Word	14	Negative	1002.52	±	59.40	
					14	Neutral	940.41	±	62.69	
					14	Positive	946.47	±	67.40	

The primary five-way mixed factorial ANOVA conducted on recognition response RT data for old vs. new correct recognitions and rejections yielded several significant main effects and interactions which are shown in Table 5.41 below. Means are shown in milliseconds. Only significant higher order interactions are reported in the text.

Table 5.41 Word Recognition Response Time analysis of word recognition ANOVA. F values, degrees of freedom, significance levels and effect sizes for interactions and main effects are shown.

Main Effects/ Interactions	df	F	p value	r
Treatment x Demand x Word Type x Valence x Glucoregulation	(2,48)	3.928	0.026	0.05
Demand x Word Type x Glucoregulation	(1,24)	7.366	0.012	0.07
Demand x Glucoregulation	(1,24)	4.85	0.037	0.06
Demand x Valence	(2,48)	9.857	<0.001	0.10
Word Type x Valence	(2,48)	4.451	0.017	0.07
Word Type	(1,24)	4.638	0.042	0.12
Valence	(2,48)	5.924	0.005	0.10

The primary five-way treatment x demand x word type x valence x glucoregulation ($F(2,48) = 3.928$, $p = .026$, $r = 0.07$) interaction was significant (see Table 5.41 above and Table 5.40 below for interaction means and SEMs) and significant pairwise comparisons are summarised in Table 5.42 below.

Glucoregulation effects of the interaction showed that after low demand encoding and following placebo better glucoregulators made faster responses than poorer glucoregulators to old positive and new negative words. Demand effects showed that faster responses were made after low demand encoding for old positive words by better regulators following glucose. Also, high demand encoding was followed by faster response times to new neutral words by better regulators and new positive words by poorer regulators after glucose. High demand encoding was followed by faster response times being achieved by poorer regulators for old neutral words following placebo. Interaction 'word type' effects revealed faster new word than old word responses by poorer regulators to neutral words following both glucose and placebo and low demand encoding and similarly to positive words following glucose. The effect of valence on the interaction showed faster processing of new positive, compared to new neutral words were made by better regulators following low demand encoding and placebo. Faster response times were also made to old positive,

compared to old neutral words, by poorer regulators following low demand encoding and glucose. There were no direct treatment effects contributing to the interaction.

Table 5.42 Word Recognition Old/New Response Reaction Time. Significant pairwise comparisons for the five-way treatment x demand x word type x valence x glucoregulation interaction. Group, pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown. Response times shown in milliseconds.

Condition / Group	Pairwise Differences Response Reaction Speeds	Mean(SEM)	t(23)=	p Value
Placebo, Low Demand, Old Words, Positive Valence	Better Faster than Poorer Glucoregulators	Better (Mean 785.65, SEM 58.56)	3.512	0.002
		Poorer (Mean 1065.90, SEM 54.22)		
Placebo, Low Demand, New Words, Negative Valence	Better Faster than Poorer Glucoregulators	Better (Mean 811.52, SEM 65.93)	2.065	0.049
		Poorer (Mean 997.19, SEM 61.08)		
Better Regulators, Glucose, Old Words, Positive Valence	Low Demand Faster than High Demand	Low (Mean 838.89, SEM 61.86)	2.13	0.044
		High (Mean 963.66, SEM 65.04)		
Better Regulators, Glucose, New Words, Neutral Valence	High Demand Faster than Low Demand	Low (Mean 923.43, SEM 92.13)	2.089	0.047
		High (Mean 818..90, SEM 66.70)		
Better Regulators, Placebo, Old Words, Positive Valence	Low Demand Faster than High Demand	Low (Mean 785.65, SEM 58.56)	3.072	0.005
		High (Mean 1015.18, SEM 82.36)		
Poorer Regulators, Glucose, New Words, Positive Valence	High Demand Faster than Low Demand	Low (Mean 984.12, SEM 72.17)	2.385	0.025
		High (Mean 884.29, SEM 60.67)		
Poorer Regulators, Placebo, Old Words, Neutral Valence	High Demand Faster than Low Demand	Low (Mean 1172.69, SEM 84.76)	2.105	0.046
		High (Mean 1028.19, SEM 60.95)		
Poorer Regulators, Glucose, Low Demand, Neutral Valence	New Word Faster than Old Word	Old Word (Mean 1190.17, SEM 98.17)	3.501	0.002
		New Word (Mean 1002.43, SEM 85.29)		
Poorer Regulators, Glucose, High Demand, Neutral Valence	New Word Faster than Old Word	Old Word (Mean 1027.23, SEM 73.54)	2.28	0.032
		New Word (Mean 907.87, SEM 61.75)		
Poorer Regulators, Placebo, Low Demand, Neutral Valence	New Word Faster than Old Word	Old Word (Mean 1172.69, SEM 84.76)	2.626	0.015
		New Word (Mean 1018.37, SEM 66.91)		
Poorer Regulators, Glucose, Low Demand, Positive Valence	New Word Faster than Old Word	Old Word (Mean 1065.90, SEM 54.22)	2.443	0.022
		New Word (Mean 918.75, SEM 56.65)		
Better Regulators, Placebo, Low Demand, New Words	Positive Faster than Neutral	Neutral Words (Mean 902.46, SEM 72.271)	2.616	0.045
		Positive Words (Mean 786.99, SEM 61.192)		
Poorer Regulators, Glucose, Low Demand, Old Words	Positive Faster than Neutral	Neutral Words (Mean1190.16, SEM 98.171)	2.645	0.043
		Positive Words (Mean 981.69, SEM 57.273)		

5.5.3.2.1 Summary of Word Recognition Old/New Behavioural Data Results

Analysis of old vs. new accuracy data showed an interaction between demand and word type such that recognition accuracy for both old and new words was greater following low demand encoding. In terms of word type, new words recognitions were more accurate old words recognitions following

both low and high demand encoding. There was also a significant main effect of glucoregulation which indicated that better regulators were more accurate than poorer regulators. Additionally, a main effect of valence identified greater accuracy for neutral, compared to positive and negative word recognitions.

Analysis of response RT data showed a significant interaction between treatment, demand, word type, valence and glucoregulation. This offered more support for the glucoregulation model used here, with better regulators making faster responses to old positive and new negative words than poorer regulators following the placebo treatment. Faster responses to old positive words were made following low demand encoding by better regulators following glucose. Following high demand encoding, faster responses to new neutral, new positive and old neutral words were made by better regulators compared to poorer regulators. Faster responses to new neutral words compared to old neutral words by poorer regulators following both glucose and placebo treatments may suggest support for more global processing being involved in processing previously seen recollections. Faster responses were seen to new positive compared to new neutral words following low demand encoding and placebo by better regulators and by poorer regulators following glucose; this may imply more effective utilisation of the glucose dose by poorer, relative to better regulators.

5.5.3.3 Word Recognition Remember/Know Subjective Judgements

Table 5.43 below shows the means and SEM for the behavioural recognition type analysis of subjective recollection or familiarity judgements. Significant effects and interactions are indicated.

Table 5.43 Word Recognition Remember/Know. Means, SEMs for the analysis of subjective recollection or familiarity judgements via the five-way mixed factorial treatment x demand x recognition type x valence x glucoregulation ANOVA. Significant effects and interactions are indicated (Gluc = Glucoregulation, Tr Treatment, Dem = Demand, RecTyp = Recognition Type, Val = Valence; (p<0.005, ***P<0.001)**

Outcome	Gluco-regulation	Treatment	Demand	Recognition Type	N	Valence	Mean	±	SEM	Significant Effects and Interactions
% of Recognitions	Better Regulators	Glucose	Low Demand Encoding	Recollection	10	Negative	34.51	±	3.23	Dem x Val *** Rec_Typ x Val ** Val ***
					10	Neutral	33.89	±	2.46	
					10	Positive	31.60	±	2.48	
				Familiarity	10	Negative	22.98	±	3.90	
					10	Neutral	47.65	±	5.95	
					10	Positive	29.37	±	6.16	
			High Demand Encoding	Recollection	10	Negative	24.78	±	2.76	
					10	Neutral	51.20	±	2.83	
					10	Positive	24.02	±	2.44	
				Familiarity	10	Negative	32.18	±	6.04	
					10	Neutral	42.58	±	5.95	
					10	Positive	25.25	±	5.39	
		Placebo	Low Demand Encoding	Recollection	10	Negative	33.21	±	2.67	
					10	Neutral	30.27	±	3.52	
					10	Positive	36.52	±	3.05	
				Familiarity	10	Negative	21.35	±	5.27	
					10	Neutral	45.44	±	6.29	
					10	Positive	33.21	±	6.57	
			High Demand Encoding	Recollection	10	Negative	32.83	±	2.26	
					10	Neutral	41.48	±	4.92	
					10	Positive	25.69	±	3.33	
				Familiarity	10	Negative	16.39	±	4.27	
					10	Neutral	57.94	±	5.36	
					10	Positive	25.66	±	5.12	
	Poorer Regulators	Glucose	Low Demand Encoding	Recollection	11	Negative	30.90	±	3.08	
					11	Neutral	32.25	±	2.34	
					11	Positive	36.85	±	2.36	
				Familiarity	11	Negative	34.06	±	3.72	
					11	Neutral	37.50	±	5.67	
					11	Positive	28.44	±	5.87	
			High Demand Encoding	Recollection	11	Negative	26.38	±	2.63	
					11	Neutral	47.79	±	2.70	
					11	Positive	25.83	±	2.33	
				Familiarity	11	Negative	23.28	±	5.76	
					11	Neutral	56.57	±	5.68	
					11	Positive	20.15	±	5.14	
		Placebo	Low Demand Encoding	Recollection	11	Negative	34.60	±	2.55	
					11	Neutral	31.74	±	3.36	
					11	Positive	33.66	±	2.91	
				Familiarity	11	Negative	33.54	±	5.02	
					11	Neutral	47.15	±	6.00	
					11	Positive	19.32	±	6.26	
			High Demand Encoding	Recollection	11	Negative	29.83	±	2.16	
					11	Neutral	45.09	±	4.69	
					11	Positive	25.09	±	3.18	
				Familiarity	11	Negative	24.47	±	4.07	
					11	Neutral	52.89	±	5.11	
					11	Positive	22.64	±	4.88	

For the five-way mixed factorial ANOVA conducted on participants subjective recollection (remember) or familiarity (know) judgements of responses to correctly recognised 'old' previously studied words. The primary treatment x demand x recognition type (R/K) x valence x glucoregulation interaction was non-significant ($F(2,38) = 1.003$, $p = .376$, $r = 0.05$). Significant main effects and

interactions are shown in Table 5.44 below. Only significant higher order interactions are reported in the text.

Table 5.44 Word Recognition Remember/Know analysis of subjective recollection or familiarity judgements. F/values, degrees of freedom, significance levels and effect sizes for significant interactions and main effects are shown.

Main Effects/ Interactions	df	F	p value	r
Demand x Valence	(2,38)	19.924	<0.001	0.24
Recognition Type x Valence	(2,38)	7.568	0.020	0.19
Valence	(2,38)	61.943	<0.001	0.44

There was a significant demand x valence interaction (F(2,38) = 19.924, p<.001, r = 0.24) (see Table 5.45 above and Table 5.45 below for interaction means and SEMs), for interaction effects of demand pairwise comparisons (see Table 5.46 Figure 5.22 below), which revealed that greater percentages of neutral recognitions were made following high demand encoding compared to low demand encoding. This was reversed for positive words for which there were more positive recognitions made following low, compared to high demand, encoding. Interaction effects of valence revealed that following both low and high demand encoding there were more neutral recognitions than both negative and positive recognitions.

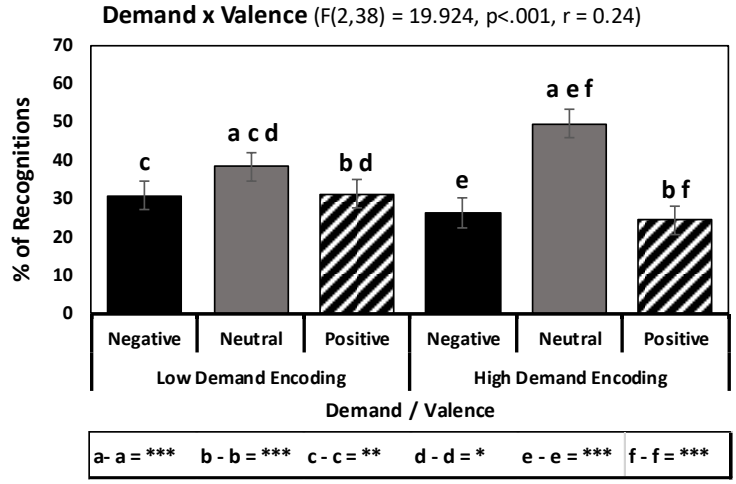
Table 5.45 Word Recognition Remember/Know. Means and SEMs depicting the demand x valence interaction.

Demand	Valence	Mean	±	SEM
Low Demand Encoding	Negative	30.644	±	1.171
	Neutral	38.236	±	1.132
	Positive	31.12	±	1.62
High Demand Encoding	Negative	26.266	±	1.455
	Neutral	49.443	±	1.457
	Positive	24.291	±	0.8

Table 5.46 Word Recognition Remember/Know analysis significant pairwise comparisons from the Demand x Valence interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition / Group	Pairwise Differences	Mean(SEM)	t(19)=	p Value
Neutral Words	High Demand > Low Demand	Low Demand (Mean 38.24, SEM 1.132)	6.784	<0.001
		High Demand (Mean 49.44 SEM 1.457)		
Positive Words	Low Demand > High Demand	Low Demand (Mean 31.12, SEM 1.620)	4.375	<0.001
		High Demand (Mean 24.29, SEM 0.800)		
Low Demand Encoding	Neutral > Negative	Neutral Words (Mean 38.24, SEM 1.132)	4.636	0.001
		Negative Words (Mean 30.64, SEM 1.171)		
Low Demand Encoding	Neutral > Positive	Neutral Words (Mean 38.24, SEM 1.132)	2.805	0.034
		Positive Words (Mean 31.12, SEM 1.620)		
High Demand Encoding	Neutral > Negative	Neutral Words (Mean 49.44, SEM 1.457)	8.275	<0.001
		Negative Words (Mean 26.27, SEM 1.455)		
High Demand Encoding	Neutral > Positive	Neutral Words (Mean 49.44, SEM 1.457)	13.625	<0.001
		Positive Words (Mean 24.29, SEM 0.800)		

Figure 5.22 Pairwise comparisons from the Demand x Valence interaction. Figure key shows pairwise comparisons and significance levels. *(*p < .05,p<.005, ***p<.001)*. Bars show standard error.**



There was a significant recognition type x valence interaction (F(2,38) = 7.568, p = .020, r = 0.19) (see Table 5.44 above and **Error! Reference source not found.** below for interaction means and SEMs), for effects of recognition type on the interaction pairwise comparisons (see Table 5.48 and Figure 5.23 below) revealed that there was a higher percentage of negative word recollection judgements than familiarity judgements. For neutral words, this pattern was reversed with more familiarity than recollection judgements being made. The impact of valence on the interaction showed that for both

recollection and familiarity judgements there were greater percentages of neutral recognitions compared to both negative and positive recognitions.

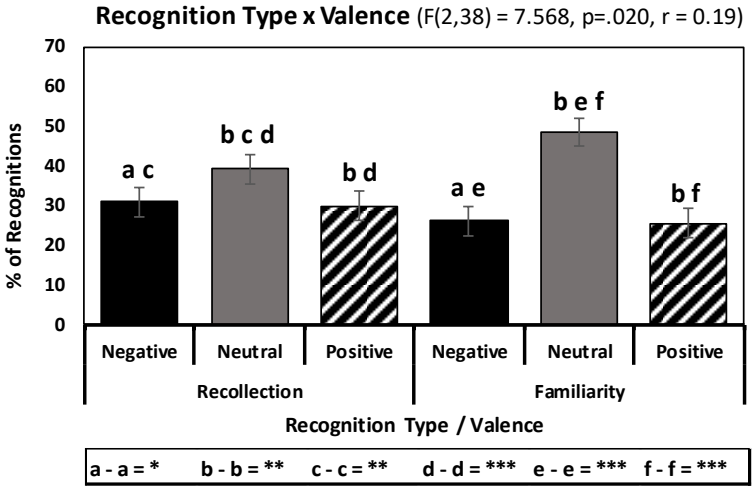
Table 5.47 Word Recognition Remember/Know analysis means and SEMs depicting the recognition type x valence interaction.

Recognition Type	Valence	Mean	±	SEM
Recollection	Negative	30.88	±	1.162
	Neutral	39.213	±	1.038
	Positive	29.907	±	0.854
Familiarity	Negative	26.029	±	1.246
	Neutral	48.466	±	1.918
	Positive	25.505	±	2.336

Table 5.48 Word Recognition Remember/Know analysis, significant pairwise comparisons from the Recognition Type x Valence interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition / Group	Pairwise Differences	Mean(SEM)	t(18)=	p Value
Negative Words	Recollection > Familiarity	Recollection (Mean 30.88, SEM 1.162)	2.683	0.015
		Familiarity (Mean 26.03, SEM 1.246)		
Neutral Words	Familiarity > Recollection	Recollection (Mean 39.21, SEM 1.038)	3.971	0.001
		Familiarity (Mean 48.47, SEM 1.918)		
Recollection	Neutral > Negative	Neutral Words (Mean 39.21, SEM 1.038)	4.103	0.002
		Negative Words (Mean 30.88, SEM 1.162)		
Recollection	Neutral > Positive	Neutral Words (Mean 39.21, SEM 1.038)	6.188	<0.001
		Positive Words (Mean 29.91, SEM 0.854)		
Familiarity	Neutral > Negative	Neutral Words (Mean 48.47, SEM 1.918)	10.025	<0.001
		Negative Words (Mean 26.03, SEM 1.162)		
Familiarity	Neutral > Positive	Neutral Words (Mean 48.47, SEM 1.918)	5.615	<0.001
		Positive Words (Mean 25.51, SEM 0.800)		

Figure 5.23 Word Recognition Remember/Know. Pairwise comparisons from the Recognition Type x Valence interaction. Figure key shows pairwise comparisons and significance levels. *(*p < .05,p<.005, ***p<.001).*Bars show standard error.**



5.5.3.3.1 Summary of Word Recognition Remember/Know Behavioural Data Results

Following both low and high demand encoding, neutral words were preferentially recognised compared to both negative and positive words with more correct neutral recognitions being made following high demand encoding. The interaction between recognition type and valence indicated that there were more negative and positive recollection judgements made relative to familiarity judgements, whereas for neutral recognitions this was reversed with less recollection than familiarity judgements being made. This suggests preferential recollection of emotional words.

5.6 Event Related Potential Results

5.6.1 Word Recognition Encoding

5.6.1.1 P1 component.

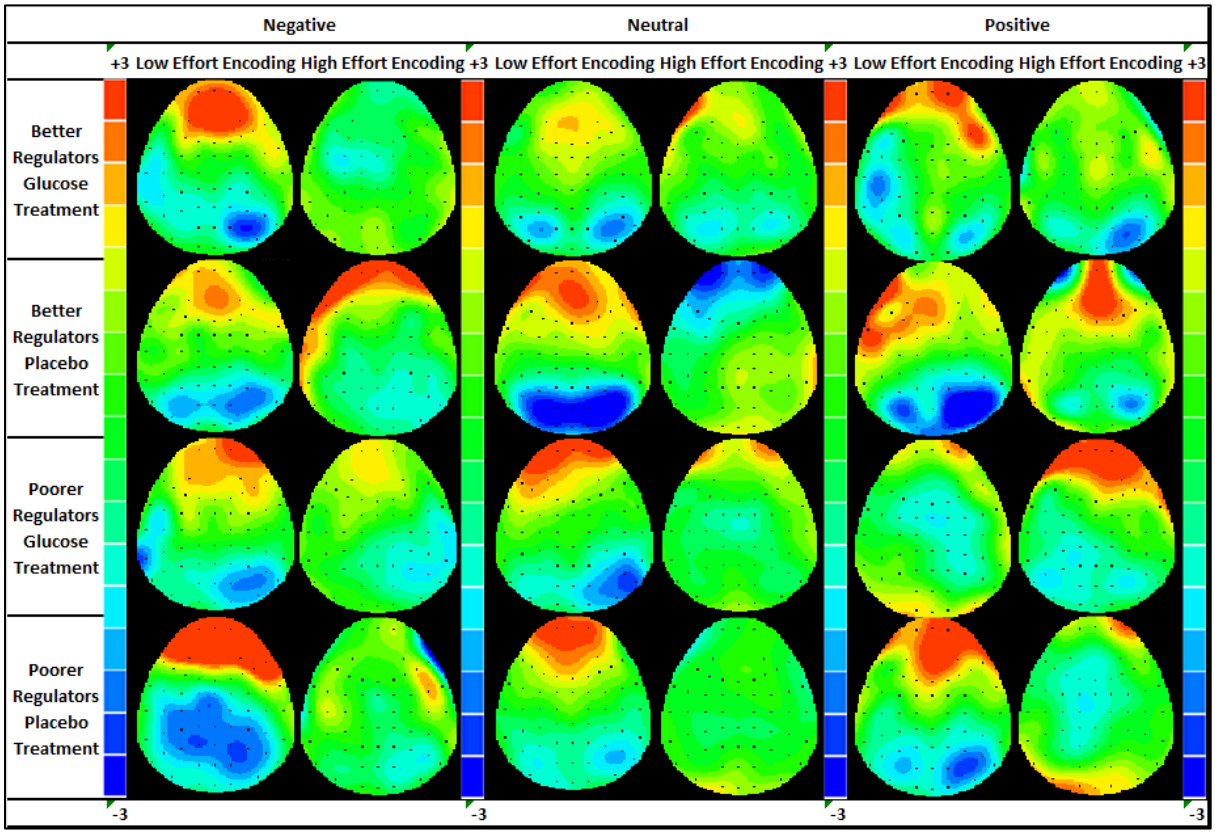
See Appendix 5.7 for the means and SEM for the ERP data for the word recognition encoding phase P1 component Appendices 5 analysis. Significant effects and interactions are indicated.

For the analysis of P1 component data in the 60 – 130ms time window the primary six-way glucoregulation x demand x treatment x valence x region x hemisphere interaction was non-significant ($F(2,46) = 0.657$, $p = .529$, $r = 0.01$). Significant main effects and interactions are shown below in Table 5.49. Only significant higher order interactions are reported in the text. Topographical maps representing the P1 component can be seen in Figure 5.24 below.

Table 5.49 Encoding Phase P1 Component. Significant main effects and interactions from the six-way glucoregulation x treatment x demand x valence x region x hemisphere ANOVA conducted on encoding data in the 60 - 130 ms time window. ANOVA F/values, degrees of freedom, significance levels and effect sizes for significant interactions and main effects are shown.

Main Effect/ Interaction	df	F	p value	r
Treatment x Region x Valence x Hemisphere	(2.58,56.68)	3.701	0.022	0.03
Glucoregulation x Region x Hemisphere	(1.40,30.76)	4.321	0.034	0.07
Demand x Valence x Hemisphere	(2.44,53.68)	3.75	0.023	0.04
Region x Hemisphere	(1.40,30.76)	9.398	0.002	0.10
Region	(1,22)	6.524	0.018	0.24
Hemisphere	(1.71,37.71)	13.666	<.001	0.14

Figure 5.24 Encoding Phase P1 Component. ERP topographies of grand average data across the 60-130 ms time window. The colour scale shows amplitude ranges from positive (red) to negative (blue) inflections from +3 to -3 microvolts.



For the four-way treatment x region x valence x hemisphere interaction (F(2.58,56.68) = 3.701, p = .022, r = 0.03) (see Table 5.49 above and Table 5.50 below for interaction means and SEMs) there were several significant pairwise comparisons, see Table 5.51 below. Regional effects on the interaction revealed enhanced P1 positivity at the posterior region for neutral and positive, but not negative words. Hemisphere effects showed the P1 amplitude being maximal following placebo and in response to positive words at the right posterior electrode. There were no treatment or valence effects.

Table 5.50 Encoding Phase P1 Component. Amplitude means and SEMs depicting the treatment x region x valence x hemisphere interaction.

Treatment	Region	Valence	Hemisphere	Mean	±	SEM
Glucose	Anterior	Negative	Left	-0.41	±	0.267
			Midline	-0.471	±	0.263
			Right	-0.369	±	0.266
		Neutral	Left	-0.272	±	0.24
			Midline	-0.418	±	0.213
			Right	-0.369	±	0.233
		Positive	Left	-0.943	±	0.317
			Midline	-0.769	±	0.253
			Right	-0.435	±	0.217
	Posterior	Negative	Left	0.463	±	0.26
			Midline	-0.286	±	0.297
			Right	0.807	±	0.387
		Neutral	Left	0.256	±	0.216
			Midline	-0.335	±	0.21
			Right	0.818	±	0.324
		Positive	Left	0.419	±	0.207
			Midline	0.173	±	0.217
			Right	0.791	±	0.31
Placebo	Anterior	Negative	Left	-0.578	±	0.207
			Midline	-0.336	±	0.207
			Right	0.004	±	0.212
		Neutral	Left	-0.537	±	0.207
			Midline	-0.376	±	0.203
			Right	-0.144	±	0.195
		Positive	Left	-0.625	±	0.297
			Midline	-0.322	±	0.266
			Right	-0.15	±	0.309
	Posterior	Negative	Left	0.361	±	0.196
			Midline	-0.203	±	0.23
			Right	0.872	±	0.279
		Neutral	Left	0.535	±	0.233
			Midline	0.027	±	0.2
			Right	0.868	±	0.275
		Positive	Left	0.438	±	0.277
			Midline	0.007	±	0.315
			Right	1.018	±	0.296

Table 5.51 Encoding Phase P1 Component. Significant pairwise comparisons from the treatment x region x valence x hemisphere interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition / Group	Pairwise Differences	Mean(SEM)	t(21)=	p Value
Glucose, Neutral, Right Hemisphere	Posterior > Anterior Region	Posterior (Mean 0.818, SEM 0.324) Anterior (Mean -0.4369 SEM 0.233)	2.330	0.029
Glucose, Positive, Left Hemisphere	Posterior > Anterior Region	Posterior (Mean 0.419, SEM 0.207) Anterior (Mean -0.943, SEM 0.317)	2.892	0.008
Glucose, Positive, Midline Hemisphere	Posterior > Anterior Region	Posterior (Mean 0.173, SEM 0.217) Anterior (Mean -0.769, SEM 0.253)	2.558	0.017
Glucose, Positive, Right Hemisphere	Posterior > Anterior Region	Posterior (Mean 0.791, SEM 0.310) Anterior (Mean -0.435, SEM 0.217)	2.507	0.020
Placebo, Negative, Left Hemisphere	Posterior > Anterior Region	Posterior (Mean 0.361, SEM 0.196) Anterior (Mean -0.578, SEM 0.207)	3.342	0.003
Placebo, Neutral, Left Hemisphere	Posterior > Anterior Region	Posterior (Mean 0.535, SEM 0.233) Anterior (Mean -0.537, SEM 0.207)	3.080	0.005
Placebo, Neutral, Right Hemisphere	Posterior > Anterior Region	Posterior (Mean 0.868, SEM 0.275) Anterior (Mean -0.144, SEM 0.195)	2.398	0.026
Placebo, Positive, Left Hemisphere	Posterior > Anterior Region	Posterior (Mean 0.438, SEM 0.277) Anterior (Mean -0.625, SEM 0.297)	2.274	0.033
Placebo, Positive, Right Hemisphere	Posterior > Anterior Region	Posterior (Mean 1.018, SEM 0.296) Anterior (Mean -0.150, SEM 0.309)	2.221	0.037
Glucose, Posterior, Negative	Left > Midline	Left (Mean 0.463, SEM 0.297) Midline (Mean -0.286, SEM 0.297)	3.901	0.002
Glucose, Posterior, Negative	Right > Midline	Right (Mean 0.807, SEM 0.387) Midline (Mean -0.286, SEM 0.297)	4.691	<0.001
Glucose, Posterior, Neutral	Left > Midline	Left (Mean 0.256, SEM 0.216) Midline (Mean -0.335, SEM 0.210)	2.897	0.025
Glucose, Posterior, Neutral	Right > Midline	Right (Mean 0.818, SEM 0.324) Midline (Mean -0.335, SEM 0.210)	4.631	<0.001
Placebo, Anterior, Negative	Right > Left	Right (Mean 0.004, SEM 0.212) Left (Mean -0.578, SEM 0.207)	4.187	0.001
Placebo, Anterior, Negative	Right > Midline	Right (Mean 0.004, SEM 0.212) Midline (Mean -0.336, SEM 0.207)	2.982	0.021
Placebo, Posterior, Negative	Left > Midline	Left (Mean 0.361, SEM 0.196) Midline (Mean -0.203, SEM 0.203)	2.938	0.023
Placebo, Posterior, Negative	Right > Midline	Right (Mean 0.872, SEM 0.279) Midline (Mean -0.203, SEM 0.203)	3.905	0.002
Placebo, Posterior, Neutral	Left > Midline	Left (Mean 0.535, SEM 0.233) Midline (Mean 0.027, SEM 0.200)	3.380	0.008
Placebo, Posterior, Neutral	Right > Midline	Right (Mean 0.868, SEM 0.275) Midline (Mean 0.027, SEM 0.200)	3.247	0.011
Placebo, Posterior, Positive	Right > Midline	Right (Mean 1.018, SEM 0.296) Midline (Mean 0.007, SEM 0.315)	4.000	0.002

Table 5.52 Encoding Phase P1 Component. Amplitude means and SEMs depicting the glucoregulation x region x hemisphere interaction.

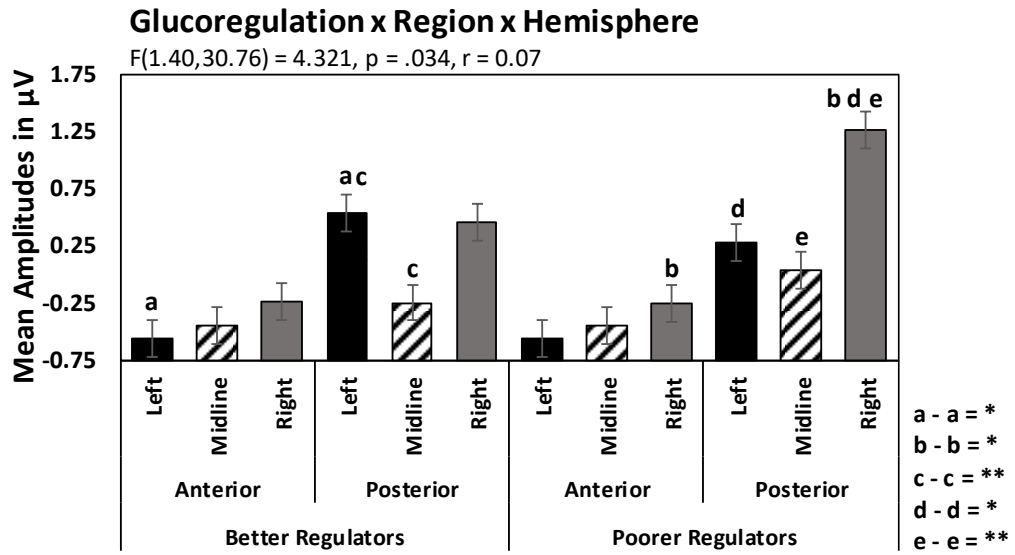
Glucoregulation	Region	Hemisphere	Mean	±	SEM
				±	
Better Regulators	Anterior	Left	-0.567	±	0.244
		Midline	-0.449	±	0.235
		Right	-0.231	±	0.238
	Posterior	Left	0.54	±	0.269
		Midline	-0.247	±	0.242
		Right	0.459	±	0.365
Poorer Regulators	Anterior	Left	-0.554	±	0.244
		Midline	-0.448	±	0.235
		Right	-0.256	±	0.238
	Posterior	Left	0.284	±	0.269
		Midline	0.042	±	0.242
		Right	1.266	±	0.365

For the three-way glucoregulation x region x hemisphere interaction ($F(1.40,30.76) = 4.321$, $p = .034$, $r = 0.07$) (see Table 5.49 above and Table 5.52 below for interaction means and SEM). There were no glucoregulation effects on the interaction. However regional comparisons showed that better regulators had enhanced left hemisphere P1 amplitudes in the posterior region relative to the anterior region, and poorer regulators had enhanced right hemisphere P1 amplitudes in the posterior region relative to the anterior region. Significant pairwise comparisons indicated regional differences between better and poorer regulators. Whilst P1 amplitudes were greater at the posterior region for glucoregulator groups there were hemisphere differences. Hemisphere pairwise differences showed that better regulators had greater left posterior relative to midline P1 amplitudes. Poorer regulators had enhanced right posterior relative to both left posterior and midline posterior P1 amplitudes. See Table 5.53 below and Figure 5.25 for significant pairwise comparisons.

Table 5.53 Encoding Phase P1 Component. Significant pairwise comparisons from the Glucoregulation x Region x Hemisphere interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition / Group	Pairwise Differences	Mean(SEM)	t(22)=	p Value
Better Regulators, Left Hemisphere	Posterior > Anterior Region	Posterior (Mean 0.540, SEM 0.269)	2.557	0.018
		Anterior (Mean -0.567 SEM 0.244)		
Poorer Regulators, Right Hemisphere	Posterior > Anterior Region	Posterior (Mean 1.266, SEM 0.365)	2.684	0.014
		Anterior (Mean -0.256, SEM 0.238)		
Better Regulators, Posterior	Left > Midline	Left (Mean 0.540, SEM 0.269)	4.164	0.001
		Midline (Mean -0.247, SEM 0.242)		
Poorer Regulators, Posterior	Right > Left	Right (Mean 1.266, SEM 0.365)	3.386	0.008
		Left (Mean 0.284, SEM 0.269)		
Poorer Regulators, Posterior	Right > Midline	Right (Mean 1.266, SEM 0.365)	3.861	0.003
		Midline (Mean 0.042, SEM 0.242)		

Figure 5.25 Pairwise comparisons from the Glucoregulation x Region x Hemisphere interaction. Figure key shows pairwise comparisons and significance levels. *(*p < .05,p<.005).* Bars show standard error.**



The three-way demand x valence x hemisphere interaction (F(2.44,53.68) = 3.75, p = .023, r = 0.04) (see Table 5.49 above and Table 5.54 below for interaction means and SEM) revealed valence effects showing that for non-tracking encoding of stimuli left hemisphere P1 amplitudes were greater

following the presentation of neutral words (Mean 0.065, SEM 0.104) compared to positive words (Mean -0.253, SEM 0.127) ($t(22) = 3.118$, $p = .015$) (see Figure 5.26a) below). There were several Hemisphere effects which indicated greater P1 amplitudes at right hemisphere electrodes, see Figure 5.26b) below and Table 5.55 below for significant pairwise comparisons. There were no direct effects of demand on the interaction.

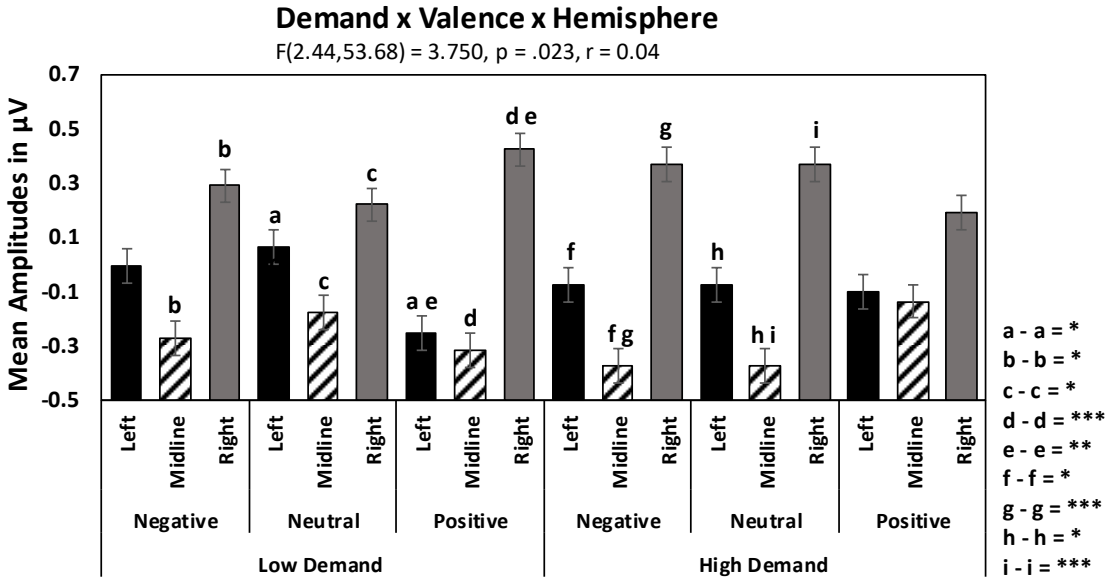
Table 5.54 Encoding Phase P1 Component. Amplitude means and SEMs depicting the demand x valence x hemisphere interaction.

Demand	Valence	Hemisphere	Mean	±	SEM
Low Demand Encoding	Negative	Left	-0.008	±	0.133
		Midline	-0.273	±	0.158
		Right	0.29	±	0.168
	Neutral	Left	0.065	±	0.104
		Midline	-0.176	±	0.106
		Right	0.22	±	0.108
	Positive	Left	-0.253	±	0.127
		Midline	-0.319	±	0.15
		Right	0.423	±	0.124
High Demand Encoding	Negative	Left	-0.074	±	0.14
		Midline	-0.374	±	0.128
		Right	0.367	±	0.123
	Neutral	Left	-0.074	±	0.14
		Midline	-0.374	±	0.128
		Right	0.367	±	0.123
	Positive	Left	-0.103	±	0.123
		Midline	-0.137	±	0.175
		Right	0.189	±	0.115

Table 5.55 Encoding Phase P1 Component. Significant pairwise comparisons from the Demand x Valence x Hemisphere interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition / Group	Pairwise Differences	Mean(SEM)	t(22)=	p Value
Low Demand, Left Hemisphere	Neutral > Positive	Neutral (Mean 0.065, SEM 0.104)	3.118	0.015
		Positive (Mean -0.253, SEM 0.127)		
Low Demand, Negative	Right > Midline	Right (Mean 0.290, SEM 0.168)	3.475	0.006
		Midline (Mean -0.273, SEM 0.158)		
Low Demand, Neutral	Right > Midline	Right (Mean 0.220, SEM 0.108)	2.712	0.038
		Midline (Mean -0.176, SEM 0.106)		
Low Demand, Positive	Right > Midline	Right (Mean 0.423, SEM 0.124)	4.787	<0.001
		Midline (Mean -0.319, SEM 0.150)		
Low Demand, Positive	Right > Left	Right (Mean 0.423, SEM 0.124)	4.447	0.001
		Left (Mean -0.243, SEM 0.127)		
High Demand, Negative	Left > Midline	Left (Mean -0.074, SEM 0.140)	2.609	0.048
		Midline (Mean -0.374, SEM 0.128)		
High Demand, Negative	Right > Midline	Right (Mean 0.367, SEM 0.123)	4.947	<0.001
		Midline (Mean -0.374, SEM 0.128)		
High Demand, Neutral	Left > Midline	Left (Mean -0.074, SEM 0.140)	2.609	0.048
		Midline (Mean -0.374, SEM 0.128)		
High Demand, Neutral	Right > Midline	Right (Mean 0.367, SEM 0.123)	4.947	<0.001
		Midline (Mean -0.374, SEM 0.128)		

Figure 5.26 Encoding Phase P1 Component. Pairwise comparisons from the Demand x Valence x Hemisphere interaction. Figure key shows pairwise comparisons and significance levels. ***(*p<.05,**p<.005,***p<.001)*****. Bars show standard error.**



5.6.1.2 N1 Component

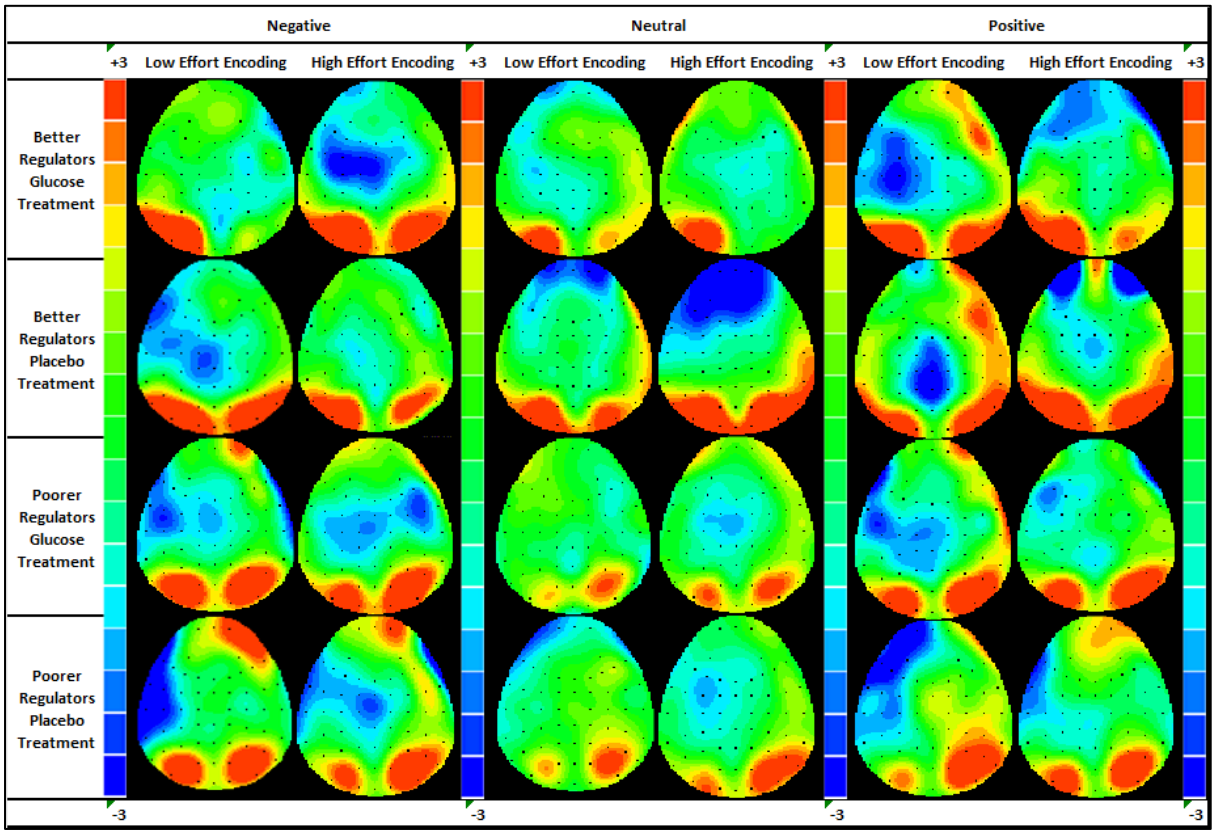
See Appendix 5.8 for the means and SEM for the ERP data for the word recognition encoding phase N1 component analysis. Significant effects and interactions are indicated.

For the analysis of the negative going N1 component data in the 130 – 220ms time window the primary six-way glucoregulation x demand x treatment x valence x region x hemisphere interaction was non-significant (F(2.26,49.63) = 1.629, p = 0.517, r =0.03). Significant main effects and interactions from the ANOVA are shown below in Table 5.56. Only significant higher order interactions are reported in the text. Topographical maps representing the N1 component can be seen in Figure 5.27 below.

Table 5.56 Encoding Phase N1 Component. Significant main effects and interactions from the six-way glucoregulation x treatment x demand x valence x region x hemisphere ANOVA conducted on encoding data in the 130 - 220 ms time window. F/values, degrees of freedom, significance levels and effect sizes for significant interactions and main effects are shown.

Main Effect/ Interaction	df	F	p value	r
Glucoregulation x Demand x Valence x Hemisphere	(3.09,68.07)	3.222	0.027	0.04
Demand x Region x Valence x Hemisphere	(2.71,59.70)	3.438	0.026	0.03
Treatment x Region x Valence x Hemisphere	(2.64,57.97)	4.512	0.009	0.04
Glucoregulation x Hemisphere	(1.63,35.89)	3.783	0.040	0.08
Region x Hemisphere	(1.38,30.24)	30.796	<.001	0.19
Treatment	(1,22)	5.890	0.024	0.07

Figure 5.27 Encoding Phase N1 Component. ERP topographies of grand average data across the 130-220 ms time window. The colour scale shows amplitude ranges from positive (red) to negative (blue) inflections from +3 to -3 microvolts.



There was a four-way Glucoregulation x Demand x Valence x Hemisphere interaction ($F(3.09,68.07) = 3.222$, $p = 0.027$, $r = 0.04$) (see Table 5.56 above and Table 5.57 below for interaction means and SEM). Pairwise comparisons (see Table 5.58 below) revealed that demand effects of the interaction showed that following high demand encoding compared to following low demand encoding there was enhanced right hemisphere N1 following the presentation of positive words to poorer regulators. Effects of hemisphere on the interaction saw poorer regulators with greater right relative to left hemisphere N1 amplitudes for positive words. Neither glucoregulation nor valence were seen to have a direct effect on the interaction. See Figure 5.28 below.

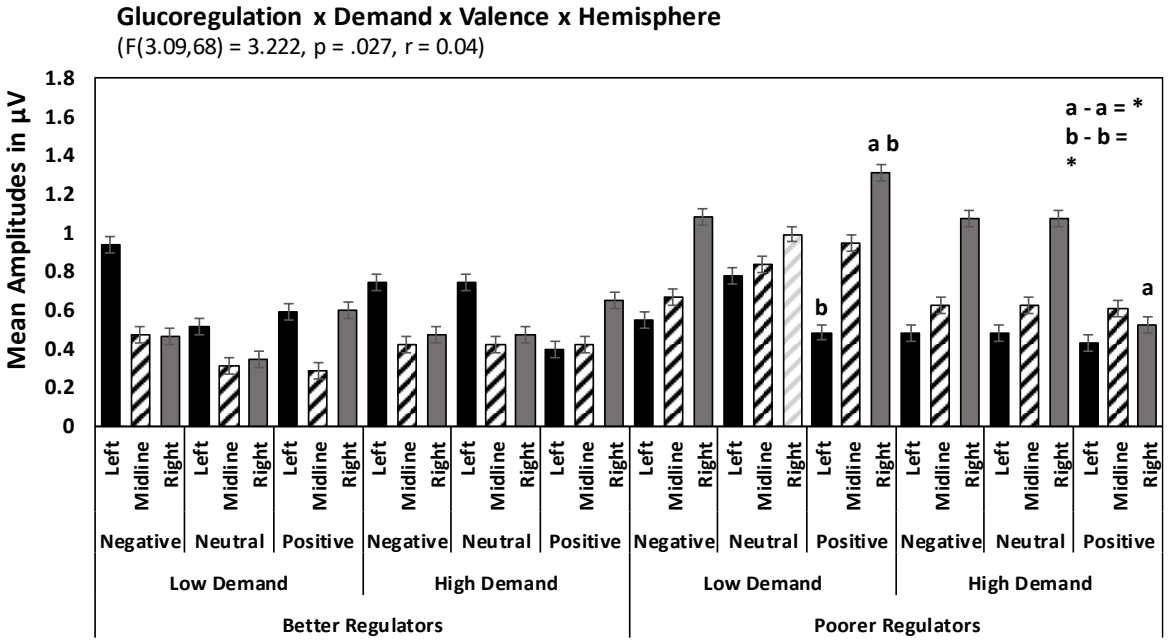
Table 5.57 Encoding Phase N1 Component. Amplitude means and SEMs depicting the glucoregulation x demand x valence x hemisphere interaction.

Glucoregulation	Demand	Valence	Hemisphere	Mean	±	SEM
Better Regulators	Low Demand Encoding	Negative	Left	0.938	±	0.236
			Midline	0.47	±	0.272
			Right	0.467	±	0.314
		Neutral	Left	0.512	±	0.178
			Midline	0.31	±	0.235
			Right	0.348	±	0.281
		Positive	Left	0.593	±	0.24
			Midline	0.287	±	0.235
			Right	0.599	±	0.251
	High Demand Encoding	Negative	Left	0.743	±	0.166
			Midline	0.422	±	0.17
			Right	0.475	±	0.21
		Neutral	Left	0.743	±	0.166
			Midline	0.422	±	0.17
			Right	0.475	±	0.21
		Positive	Left	0.396	±	0.193
			Midline	0.422	±	0.198
			Right	0.652	±	0.169
Poorer Regulators	Low Demand Encoding	Negative	Left	0.551	±	0.236
			Midline	0.67	±	0.272
			Right	1.086	±	0.314
		Neutral	Left	0.775	±	0.178
			Midline	0.837	±	0.235
			Right	0.994	±	0.281
		Positive	Left	0.485	±	0.24
			Midline	0.944	±	0.235
			Right	1.316	±	0.251
	High Demand Encoding	Negative	Left	0.484	±	0.166
			Midline	0.623	±	0.17
			Right	1.077	±	0.21
		Neutral	Left	0.484	±	0.166
			Midline	0.623	±	0.17
			Right	1.077	±	0.21
		Positive	Left	0.428	±	0.193
			Midline	0.608	±	0.198
			Right	0.52	±	0.169

Table 5.58 Encoding Phase N1 Component. Significant pairwise comparisons from the Glucoregulation x Demand x Valence x Hemisphere interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition / Group	Pairwise Differences	Mean(SEM)	t(21)=	p Value
Poorer Regulators, Positive, Right Hemisphere	High Demand > Low Demand	Low (Mean 1.316, SEM 0.251)	3.034	0.006
		High Demand (Mean 0.520, SEM 0.169)		
Poorer Regulators, Low Demand, Positive	Left > Right	Left (Mean 0.485, SEM 0.240)	3.272	0.01
		Right (Mean 1.316 SEM 0.251)		

Figure 5.28 Encoding Phase N1 Component. Glucoregulation x Demand x Valence x Hemisphere interaction showing enhanced amplitudes at right hemisphere electrodes for poorer regulators following high demand encoding of positive words. Figure key shows pairwise comparisons and significance levels.



(*p<.05). Bars show standard error.

There was a significant four-way Demand x Region x Valence x Hemisphere interaction (F(2.71,59.70) = 3.438, p = .026, r =0.03) (see Table 5.56 above and Table 5.59 below for interaction means and SEM), Significant pairwise comparisons can be seen below in Table 5.60. Region effects revealed that during low demand encoding there were higher anterior than posterior midline N1 midline amplitudes elicited by negative, neutral, and positive words. Similarly, during high demand encoding there were also higher anterior than posterior midline N1 midline hemisphere amplitudes elicited by negative and neutral, but not positive words.

Table 5.59 Encoding Phase N1 Component. Amplitude means and SEMs depicting the demand x region x valence x hemisphere interaction.

Demand	Region	Valence	Hemisphere	Mean	±	SEM
Low Demand Encoding	Anterior	Negative	Left	0.962	±	0.277
			Midline	1.276	±	0.276
			Right	0.739	±	0.256
		Neutral	Left	0.794	±	0.233
			Midline	1.102	±	0.259
			Right	0.52	±	0.254
		Positive	Left	0.757	±	0.325
			Midline	1.287	±	0.293
			Right	0.854	±	0.302
	Posterior	Negative	Left	0.527	±	0.285
			Midline	-0.136	±	0.408
			Right	0.814	±	0.498
		Neutral	Left	0.493	±	0.283
			Midline	0.045	±	0.28
			Right	0.821	±	0.373
		Positive	Left	0.321	±	0.287
			Midline	-0.056	±	0.32
			Right	1.06	±	0.363
High Demand Encoding	Anterior	Negative	Left	0.929	±	0.171
			Midline	1.397	±	0.206
			Right	0.687	±	0.221
		Neutral	Left	0.929	±	0.171
			Midline	1.397	±	0.206
			Right	0.687	±	0.221
		Positive	Left	0.288	±	0.325
			Midline	0.794	±	0.225
			Right	0.424	±	0.197
	Posterior	Negative	Left	0.297	±	0.228
			Midline	-0.352	±	0.175
			Right	0.865	±	0.263
		Neutral	Left	0.297	±	0.228
			Midline	-0.352	±	0.175
			Right	0.865	±	0.263
		Positive	Left	0.536	±	0.222
			Midline	0.236	±	0.254
			Right	0.749	±	0.275

Table 5.60 Encoding Phase N1 Component. Significant pairwise comparisons from the Demand x Region x Valence x Hemisphere interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition / Group	Pairwise Differences	Mean(SEM)	t(22)=	p Value
Low Demand, Negative, Midline Hemisphere	Posterior > Anterior Region	Anterior (Mean 1.276, SEM 0.276)	2.430	0.024
		Posterior (Mean -0.136, SEM 0.408)		
Low Demand, Neutral, Midline Hemisphere	Posterior > Anterior Region	Anterior (Mean 1.102, SEM 0.259)	2.487	0.021
		Posterior (Mean 0.045, SEM 0.280)		
Low Demand, Positive, Midline Hemisphere	Posterior > Anterior Region	Anterior (Mean 1.287, SEM 0.293)	2.605	0.016
		Posterior (Mean -0.056, SEM 0.320)		
High Demand, Negative, Midline Hemisphere	Posterior > Anterior Region	Anterior (Mean 1.397, SEM 0.206)	5.869	<0.001
		Posterior (Mean -0.352, SEM 0.175)		
High Demand, Neutral, Midline Hemisphere	Posterior > Anterior Region	Anterior (Mean 1.397, SEM 0.206)	5.869	<0.001
		Posterior (Mean -0.352, SEM 0.175)		

For the four-way Treatment x Region x Valence x Hemisphere interaction ($F(2.64,57.97) = 4.512$, $p = .009$, $r = 0.04$) (see Table 5.56 above and Table 5.61 below for interaction means and SEM), there were several significant pairwise comparisons which can be seen in Table 5.62 below. Interaction treatment differences (see Figure 5.29 below) were seen across anterior locations but not for posterior locations. For encoding of negative words there was an enhanced right anterior N1 following glucose relative to placebo. For encoding of neutral words there was an enhanced midline anterior N1 following glucose relative to placebo. Also, for neutral word encoding, there was a higher right anterior N1 following glucose relative to placebo. Interaction regional differences showed enhanced N1 amplitudes at posterior electrodes relative to anterior electrodes following both glucose and placebo and across all three valences. Interaction hemisphere effects showed enhanced anterior right hemisphere N1 amplitudes following glucose, but this pattern was not seen following placebo. Also following both glucose and placebo, the posterior N1 was higher at midline relative to left and right hemispheres. There were no effects of valence on the interaction.

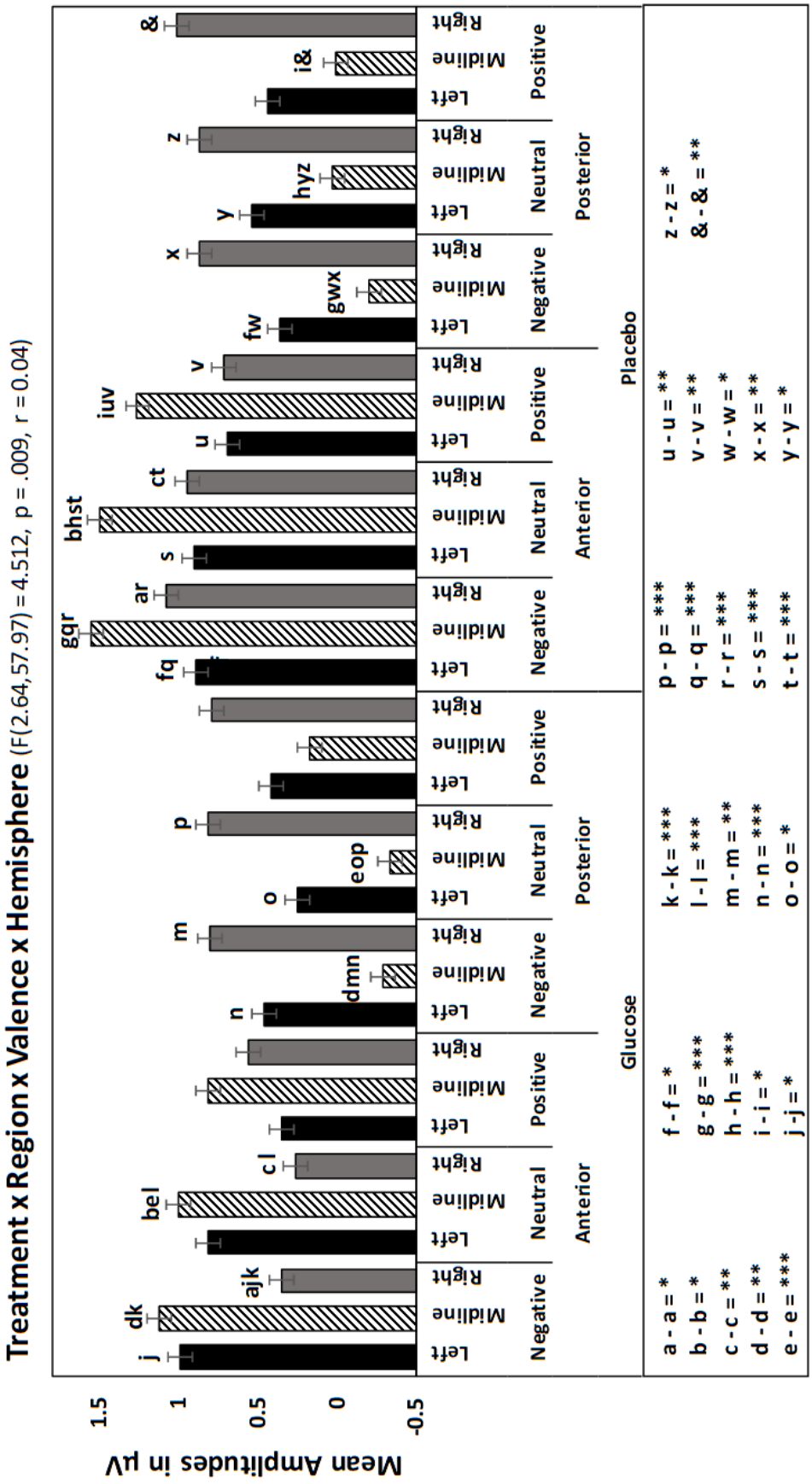
Table 5.61 Encoding Phase N1 Component. Amplitude means and SEMs depicting the treatment x region x valence x hemisphere interaction.

Treatment	Region	Valence	Hemisphere	Mean	±	SEM
Glucose	Anterior	Negative	Left	0.995	±	0.205
			Midline	1.122	±	0.218
			Right	0.347	±	0.271
		Neutral	Left	0.816	±	0.194
			Midline	0.998	±	0.2
			Right	0.26	±	0.247
		Positive	Left	0.347	±	0.357
			Midline	0.819	±	0.218
			Right	0.56	±	0.192
	Posterior	Negative	Left	0.463	±	0.26
			Midline	-0.286	±	0.297
			Right	0.807	±	0.387
		Neutral	Left	0.256	±	0.216
			Midline	-0.335	±	0.21
			Right	0.818	±	0.324
		Positive	Left	0.419	±	0.207
			Midline	0.173	±	0.217
			Right	0.791	±	0.31
Placebo	Anterior	Negative	Left	0.897	±	0.188
			Midline	1.551	±	0.195
			Right	1.078	±	0.17
		Neutral	Left	0.906	±	0.206
			Midline	1.501	±	0.192
			Right	0.947	±	0.202
		Positive	Left	0.698	±	0.346
			Midline	1.262	±	0.31
			Right	0.718	±	0.321
	Posterior	Negative	Left	0.361	±	0.196
			Midline	-0.203	±	0.23
			Right	0.872	±	0.279
		Neutral	Left	0.535	±	0.233
			Midline	0.027	±	0.2
			Right	0.868	±	0.275
		Positive	Left	0.438	±	0.277
			Midline	0.007	±	0.315
			Right	1.018	±	0.296

Table 5.62 Encoding Phase N1 Component. Significant pairwise comparisons from the Treatment x Region x Valence x Hemisphere interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition / Group	Pairwise Differences	Mean(SEM)	t(22)=	p Value
Anterior, Negative, Right Hemisphere	Glucose > Placebo	Glucose (Mean 0.347, SEM 0.271) Placebo (Mean 1.078 SEM 0.170)	2.529	0.019
Anterior, Neutral, Midline Hemisphere	Glucose > Placebo	Glucose (Mean 0.998, SEM 0.200) Placebo (Mean 1.501 SEM 0.192)	2.936	0.008
Anterior, Neutral, Right Hemisphere	Glucose > Placebo	Glucose (Mean 0.260, SEM 0.247) Placebo (Mean 0.947 SEM 0.202)	3.181	0.004
Glucose, Negative, Midline Hemisphere	Posterior > Anterior Region	Posterior (Mean -0.286, SEM 0.297) Anterior (Mean 1.122 SEM 0.218)	3.259	0.004
Glucose, Neutral, Midline Hemisphere	Posterior > Anterior Region	Posterior (Mean -0.335, SEM 0.210) Anterior (Mean 0.998, SEM 0.200)	4.370	<0.001
Placebo, Negative, Left Hemisphere	Posterior > Anterior Region	Posterior (Mean 0.361, SEM 0.196) Anterior (Mean 0.897, SEM 0.188)	2.086	0.049
Placebo, Negative, Midline Hemisphere	Posterior > Anterior Region	Posterior (Mean -0.203, SEM 0.230) Anterior (Mean 1.551, SEM 0.195)	5.583	<0.001
Placebo, Neutral, MIdline Hemisphere	Posterior > Anterior Region	Posterior (Mean 0.027, SEM 0.200) Anterior (Mean 0.1501, SEM 0.192)	4.589	<0.001
Placebo, Positive, MIdline Hemisphere	Posterior > Anterior Region	Posterior (Mean 0.007, SEM 0.315) Anterior (Mean 1.262, SEM 0.310)	2.300	0.031
Glucose, Negative, Anterior	Right > Left	Right (Mean 0.347, SEM 0.271) Left (Mean 0.995, SEM 0.205)	2.901	0.025
Glucose, Negative, Anterior	Right > Midline	Right (Mean 0.347, SEM 0.271) Midline (Mean 1.122, SEM 0.218)	4.905	<0.001
Glucose, Neutral, Anterior	Right > Midline	Right (Mean 0.560, SEM 0.192) Midline (Mean 0.819, SEM 0.218)	4.642	<0.001
Glucose, Negative, Posterior	Midline > Right	Midline (Mean -0.286, SEM 0.297) Right (Mean 0.463, SEM 0.260)	3.901	0.002
Glucose, Negative, Posterior	Midline > Left	Midline (Mean -0.286, SEM 0.297) Left (Mean 0.807, SEM 0.387)	4.691	<0.001
Glucose, Neutral, Posterior	Midline > Left	Midline (Mean -0.335, SEM 0.210) Left (Mean 0.256, SEM 0.216)	2.897	0.025
Glucose, Neutral, Posterior	Midline > Right	Midline (Mean -0.335, SEM 0.210) Right (Mean 0.818, SEM 0.324)	4.631	<0.001
Placebo, Negative, Anterior	Left > Midline	Left (Mean 0.897, SEM 0.188) Midline (Mean 1.551, SEM 0.195)	4.671	<0.001
Placebo, Negative, Anterior	Right > Midline	Right (Mean 1.078, SEM 0.170) Midline (Mean 1.551, SEM 0.195)	5.130	<0.001
Placebo, Neutral, Anterior	Left > Midline	Left (Mean 0.906, SEM 0.206) Midline (Mean 1.501, SEM 0.192)	5.767	<0.001
Placebo, Neutral, Anterior	Right > Midline	Right (Mean 0.947, SEM 0.202) Midline (Mean 1.501, SEM 0.192)	6.156	<0.001
Placebo, Positive, Anterior	Left > Midline	Left (Mean 0.698, SEM 0.346) Midline (Mean 1.262, SEM 0.310)	4.338	0.001
Placebo, Positive, Anterior	Right > Midline	Right (Mean 0.718, SEM 0.321) Midline (Mean 1.262, SEM 0.310)	3.627	0.005
Placebo, Negative, Posterior	Midline > Left	Midline (Mean -0.203, SEM 0.230) Left (Mean 0.361, SEM 0.196)	2.938	0.023
Placebo, Negative, Posterior	Midline > Right	Midline (Mean -0.203, SEM 0.230) Right (Mean 0.872, SEM 0.279)	3.905	0.002
Placebo, Neutral, Posterior	Midline > Left	Midline (Mean 0.027, SEM 0.200) Left (Mean 0.535, SEM 0.233)	3.380	0.008
Placebo, Neutral, Posterior	Midline > Right	Midline (Mean 0.027, SEM 0.200) Right (Mean 0.868, SEM 0.275)	3.247	0.011
Placebo, Positive, Posterior	Midline > Right	Midline (Mean 0.007, SEM 0.315) Right (Mean 1.018, SEM 0.296)	4.000	0.002

Figure 5.29 Encoding Phase N1 Component. Significant pairwise treatment comparisons from the four-way Treatment x Region x Valence x Hemisphere interaction. See figure key for significance levels (p<.05;**p<.005,***p<.001)* . Bars show standard error.**



Finally, the main effect of Treatment (F(1.22) = 5.890, p = .024, r =0.07), see Table 5.56 above, revealed enhanced N1 amplitudes following glucose (Mean 0.521, SEM 0.109) in comparison to placebo (Mean 0.749, SEM 0.098).

5.6.1.3 P3 component

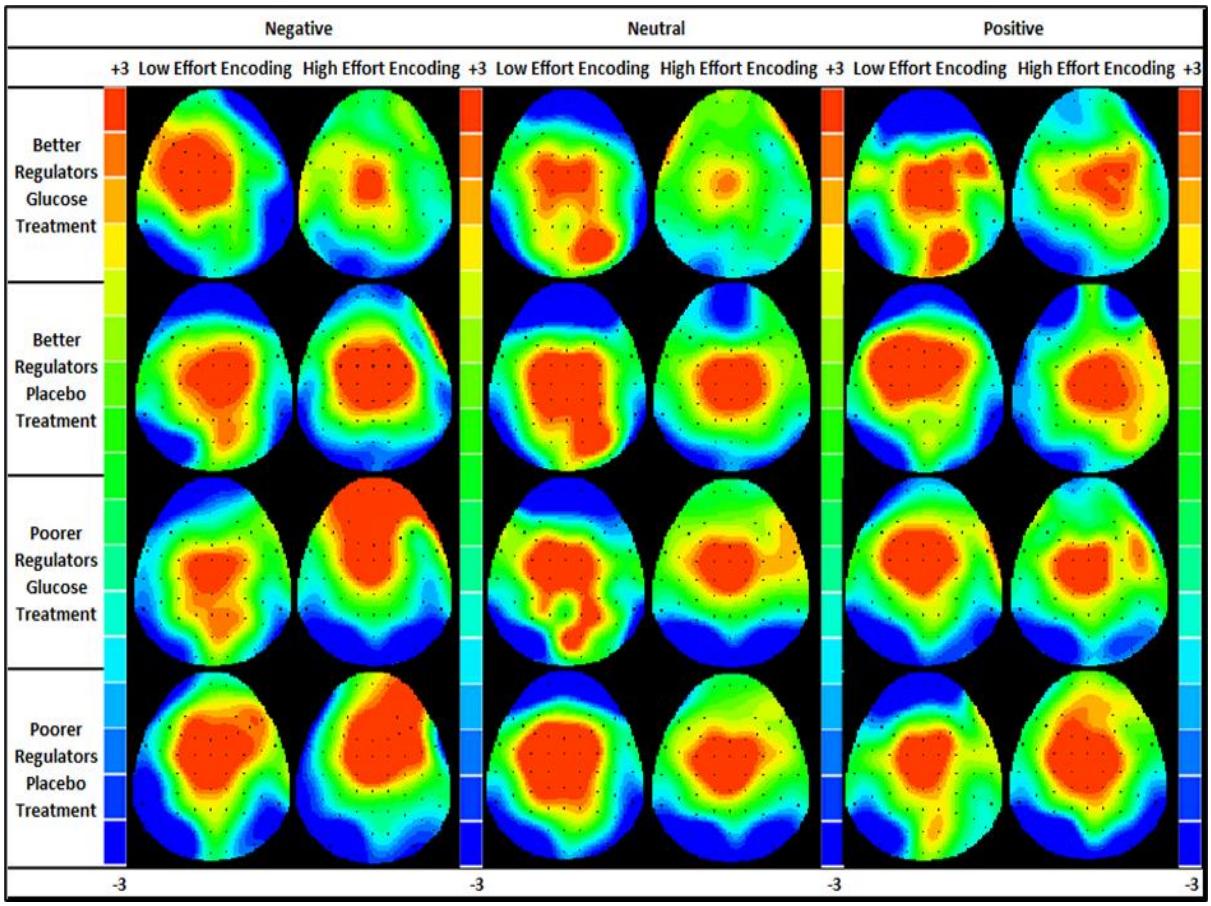
See Appendix 5.9 for the means and SEM for the ERP data for the word recognition encoding phase P3 component analysis. Significant effects and interactions are indicated.

For the analysis of positive going P3 component data in the 210 – 330ms time window the primary six-way glucoregulation x demand x treatment x region x valence x hemisphere interaction was non-significant (F(2.66,58.57) = 1.625, p = .198). Significant main effects and interactions are shown below in Table 5.63. Only significant higher order interactions are reported in the text. Topographical maps representing the P3 component can be seen in Figure 5.30 below.

Table 5.63 Encoding Phase P3 Component. Significant main effects and interactions from the six-way glucoregulation x treatment x demand x valence x region x hemisphere ANOVA conducted on encoding data in the 210 - 330 ms time window. ANOVA F values, degrees of freedom, significance levels and effect sizes for significant interactions and main effects are shown.

Main Effect/ Interaction	df	F	p value	r
Demand x Region x Valence x Hemisphere	(2.43,53.38)	4.006	0.018	0.04
Treatment x Hemisphere x Glucoregulation	(1.95,42.86)	3.954	0.027	0.04
Demand x Region x Valence	(1.79,39.39)	4.242	0.025	0.08
Treatment x Region	(1,22)	4.62	0.043	0.11
Demand x Valence	(1.65,36.29)	3.83	0.038	0.04
Demand x Region	(1,22)	6.885	0.016	0.18
Demand x Hemisphere	(1.83,40.26)	14.078	<0.001	0.09
Region x Hemisphere	(1.96,43.03)	27.067	<.001	0.18
Treatment	(1,22)	5.163	0.033	0.05
Region	(1,22)	22.614	<.001	0.42
Valence	(1.33,29.32)	12.385	0.001	0.09
Hemisphere	(1.57,34.62)	10.771	0.001	0.16

Figure 5.30 Encoding Phase P3 Component. ERP topographies of grand average encoding data for P3 component across the 210-330 ms time window. The colour scale shows amplitude ranges from positive (red) to negative (blue) inflections from +3 to -3 microvolts.



The significant four-way demand x region x valence x hemisphere interaction ($F(2.43,53.38) = 4.006$, $p = .018$, $r = 0.04$) (see Table 5.63 above and Table 5.64 below for interaction means and SEM), for significant pairwise comparisons (See Table 5.65 below). Interaction effects of demand revealed significantly enhanced anterior P3 positivity during high demand encoding. Conversely, posterior P3 amplitudes were enhanced during low demand encoding. Regional effects on the interaction showed widespread enhanced posterior P3 positivity. Interaction valence effects revealed enhanced midline and right hemisphere P3 amplitudes elicited by neutral words compared to positive words during high demand encoding. There were also several significant, hemisphere effects on the interaction although no meaningful interpretation of these was apparent within the interaction.

Table 5.64 Encoding Phase P3 Component. Amplitude means and SEMs depicting the demand x region x valence x hemisphere interaction.

Demand	Region	Valence	Hemisphere	Mean	±	SEM
Low Demand Encoding	Anterior	Negative	Left	-0.215	±	0.241
			Midline	-0.437	±	0.286
			Right	-0.413	±	0.257
		Neutral	Left	-0.846	±	0.222
			Midline	-1.032	±	0.185
			Right	-0.932	±	0.212
		Positive	Left	-0.807	±	0.238
			Midline	-1.022	±	0.195
			Right	-0.813	±	0.216
	Posterior	Negative	Left	0.982	±	0.261
			Midline	0.361	±	0.311
			Right	1.501	±	0.348
		Neutral	Left	1.434	±	0.286
			Midline	0.384	±	0.297
			Right	2.061	±	0.296
		Positive	Left	0.912	±	0.285
			Midline	0.142	±	0.388
			Right	1.881	±	0.301
High Demand Encoding	Anterior	Negative	Left	0.109	±	0.13
			Midline	0.504	±	0.174
			Right	0.103	±	0.209
		Neutral	Left	0.109	±	0.13
			Midline	0.504	±	0.174
			Right	0.103	±	0.209
		Positive	Left	-0.77	±	0.347
			Midline	-0.452	±	0.219
			Right	-0.456	±	0.197
	Posterior	Negative	Left	0.309	±	0.172
			Midline	0.458	±	0.257
			Right	1.329	±	0.201
		Neutral	Left	0.309	±	0.172
			Midline	0.458	±	0.257
			Right	1.329	±	0.201
		Positive	Left	0.658	±	0.184
			Midline	0.215	±	0.34
			Right	1.218	±	0.261

Table 5.65 Encoding Phase P3 Component. Significant pairwise comparisons from the four-way Demand x Region x Valence x Hemisphere interaction. (Pairwise differences, means and SEMs, t values and p values are indicated).

Condition / Group	Pairwise Differences	Mean(SEM)	t(22)=	p Value
Anterior, Negative, Midline Hemisphere	High > Low	Low Demand (Mean -0.437, SEM 0.286) High Demand (Mean 0.504, SEM 0.174)	2.950	0.007
Anterior, Neutral, Left Hemisphere	High > Low	Low Demand (Mean -0.846, SEM 0.222) High Demand (Mean 0.109, SEM 0.130)	3.655	0.001
Anterior, Neutral, Midline Hemisphere	High > Low	Low Demand (Mean -1.032, SEM 0.285) High Demand (Mean 0.504, SEM 0.174)	6.449	<0.001
Anterior, Neutral, Right Hemisphere	High > Low	Low Demand (Mean -0.932, SEM 0.212) High Demand (Mean 0.103, SEM 0.209)	4.349	<.001
Anterior, Positive, Midline Hemisphere	High > Low	Low Demand (Mean -1.022, SEM 0.195) High Demand (Mean -0.452, SEM 0.219)	2.500	0.020
Posterior, Neutral, Midline Hemisphere	Low > High	Low Demand (Mean 0.982, SEM 0.261) High Demand (Mean 0.309, SEM 0.172)	2.667	0.014
Posterior, Neutral, Left Hemisphere	Low > High	Low Demand (Mean 1.434, SEM 0.286) High Demand (Mean 0.309, SEM 0.172)	4.891	<0.001
Posterior, Neutral, Right Hemisphere	Low > High	Low Demand (Mean 2.061, SEM 0.296) High Demand (Mean 1.329, SEM 0.201)	2.485	0.021
Posterior, Neutral, Midline Hemisphere	Low > High	Low Demand (Mean 1.881, SEM 0.301) High Demand (Mean 1.218, SEM 0.261)	2.691	0.013

Continued.

Low Demand, Negative, Left Hemisphere	Posterior > Anterior	Posterior (Mean 0.982, SEM 0.261) Anterior (Mean -0.215, SEM 0.241)	2.574	0.017
Low Demand, Negative, Right Hemisphere	Posterior > Anterior	Posterior (Mean 1.501, SEM 0.348) Anterior (Mean -0.413, SEM 0.257)	3.407	0.003
Low Demand, Neutral, Left Hemisphere	Posterior > Anterior	Posterior (Mean 1.434, SEM 0.286) Anterior (Mean -0.846 SEM 0.222)	4.957	<0.001
Low Demand, Neutral, Midline Hemisphere	Posterior > Anterior	Posterior (Mean 0.384, SEM 0.297) Anterior (Mean -1.032, SEM 0.185)	3.420	0.002
Low Demand, Neutral, Right Hemisphere	Posterior > Anterior	Posterior (Mean 2.061, SEM 0.296) Anterior (Mean -0.932, SEM 0.212)	6.899	<0.001
Low Demand, Positive, Left Hemisphere	Posterior > Anterior	Posterior (Mean 0.791, SEM 0.310) Anterior (Mean -0.435, SEM 0.217)	4.016	0.001
Low Demand, Positive, Midline Hemisphere	Posterior > Anterior	Posterior (Mean 0.142, SEM 0.388) Anterior (Mean -1.022, SEM 0.195)	2.192	0.039
Low Demand, Positive, Right Hemisphere	Posterior > Anterior	Posterior (Mean 1.881, SEM 0.301) Anterior (Mean -0.813, SEM 0.216)	5.842	<0.001
High Demand, Negative, Right Hemisphere	Posterior > Anterior	Posterior (Mean 1.329, SEM 0.201) Anterior (Mean 0.103, SEM 0.209)	3.523	0.002
High Demand, Neutral, Right Hemisphere	Posterior > Anterior	Posterior (Mean 1.329, SEM 0.201) Anterior (Mean 0.103, SEM 0.209)	3.253	0.002
High Demand, Positive, Left Hemisphere	Posterior > Anterior	Posterior (Mean 0.658, SEM 0.184) Anterior (Mean -0.770, SEM 0.347)	2.994	0.007
High Demand, Positive, Right Hemisphere	Posterior > Anterior	Posterior (Mean 1.218, SEM 0.261) Anterior (Mean -0.456, SEM 0.197)	4.503	<0.001
High Demand, Anterior, Midline Hemisphere	Neutral > Positive	Neutral (Mean 0.504, SEM 0.174) Positive (Mean -0.452, SEM 0.219)	3.476	0.006
High Demand, Anterior, Right Hemisphere	Neutral > Positive	Neutral (Mean 0.103, SEM 0.209) Positive (Mean -0.456, SEM 0.197)	2.809	0.031
Low Demand, Posterior, Negative	Left > Midline	Left (Mean 0.982, SEM 0.261) Midline (Mean 0.361, SEM 0.261)	3.653	0.004
Low Demand, Posterior, Negative	Right > Midline	Right (Mean 1.501, SEM 0.348) Midline (Mean 0.361, SEM 0.261)	4.273	0.001
Low Demand, Posterior, Neutral	Left > Midline	Left (Mean 1.434, SEM 0.286) Midline (Mean 0.384, SEM 0.297)	5.048	<0.001
Low Demand, Posterior, Neutral	Right > Midline	Right (Mean 2.061, SEM 0.296) Midline (Mean 0.384, SEM 0.297)	5.884	<0.001
Low Demand, Posterior, Positive	Left > Midline	Left (Mean 0.912, SEM 0.285) Midline (Mean 0.142, SEM 0.285)	3.889	0.002
Low Demand, Posterior, Positive	Right > Midline	Right (Mean 1.881, SEM 0.301) Midline (Mean 0.142, SEM 0.285)	5.976	<0.001
High Demand, Anterior, Negative	Left > Midline	Left (Mean 0.109, SEM 0.174) Midline (Mean 0.504, SEM 0.174)	3.110	0.015
High Demand, Posterior, Negative	Right > Left	Right (Mean 1.329, SEM 0.172) Left (Mean 0.309, SEM 0.172)	4.529	<0.001
High Demand, Posterior, Negative	Right > Midline	Right (Mean 1.329, SEM 0.172) Midline (Mean 0.459, SEM 0.257)	3.541	0.006
High Demand, Posterior, Neutral	Right > Midline	Right (Mean 1.329, SEM 0.201) Midline (Mean 0.458, SEM 0.257)	3.541	0.006
High Demand, Posterior, Neutral	Right > Left	Right (Mean 1.329, SEM 0.201) Left (Mean 0.309, SEM 0.172)	4.529	<0.001
High Demand, Posterior, Positive	Right > Left	Right (Mean 1.218, SEM 0.184) Left (Mean 0.658, SEM 0.184)	2.671	0.042
High Demand, Posterior, Positive	Right > Midline	Right (Mean 1.218, SEM 0.184) Midline (Mean 0.215, SEM 0.340)	4.268	0.001

There was a three-way treatment x hemisphere x glucoregulation interaction ($F(1.95,42.86) = 3.954$, $p = .027$, $r = 0.04$) (see Table 5.63 above and Table 5.66 below for interaction means and SEM). Pairwise comparisons (see Table 5.67 below) revealed that treatment effects on the interaction showed that following placebo poorer regulators had enhanced right hemisphere P3 positivity relative to glucose. Hemisphere effects showed enhanced right relative to midline hemisphere P3 amplitudes following both glucose and placebo for better regulators. There were no direct effects of glucoregulation on the interaction. See Figure 5.31 below.

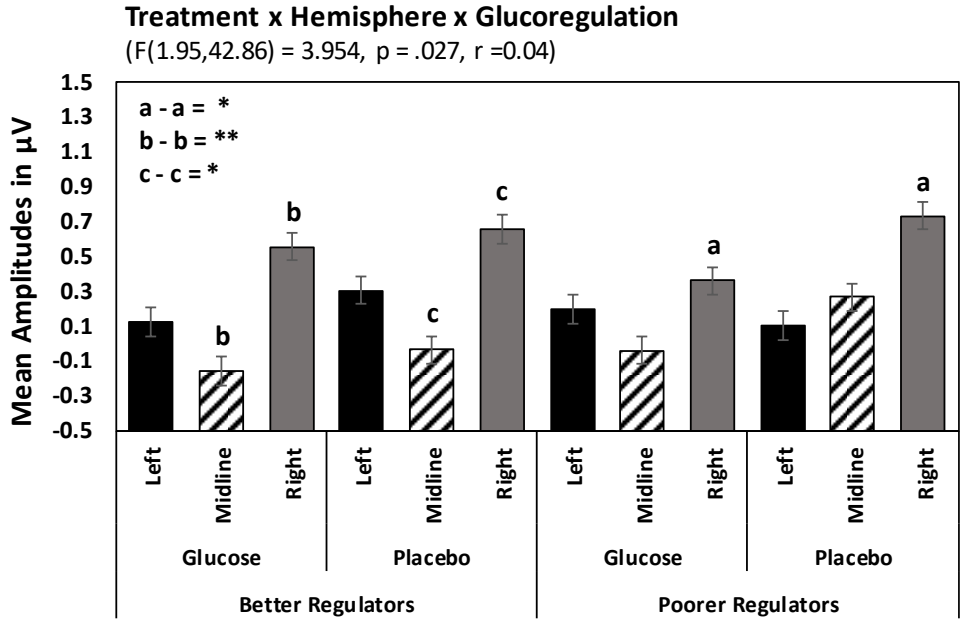
Table 5.66 Encoding Phase P3 Component. Amplitude means and SEMs depicting the treatment x hemisphere x glucoregulation interaction.

Glucoregulation	Treatment	Hemisphere	Mean	±	SEM
Better Regulators	Glucose	Left	0.124	±	0.134
		Midline	-0.158	±	0.13
		Right	0.556	±	0.105
	Placebo	Left	0.304	±	0.134
		Midline	-0.039	±	0.193
		Right	0.655	±	0.181
Poorer Regulators	Glucose	Left	0.195	±	0.134
		Midline	-0.041	±	0.13
		Right	0.358	±	0.105
	Placebo	Left	0.104	±	0.134
		Midline	0.265	±	0.193
		Right	0.734	±	0.181

Table 5.67 P3 component significant pairwise comparisons from the Treatment x Hemisphere x Glucoregulation interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition / Group	Pairwise Differences	Mean(SEM)	t(21)=	p Value
Poorer Regulators, Right Hemisphere	Placebo > Glucose	Glucose (Mean 0.358, SEM 0.105)	2.915	0.008
		Placebo (Mean 0.734, SEM 0.181)		
Better Regulators, Glucose	Right > Midline	Right (Mean 0.556, SEM 0.105)	4.127	0.001
		Midline (Mean -0.158, SEM 0.130)		
Better Regulators, Placebo	Right > Midline	Right (Mean 0.655, SEM 0.181)	2.941	0.023
		Midline (Mean -0.039, SEM 0.193)		

Figure 5.31 Encoding Phase P3 Component. Significant pairwise comparisons from the Treatment x Hemisphere x Glucoregulation interaction. Figure key shows pairwise comparisons and significance levels. (*p<.05,p<.01).* Bars show standard error.**



For the treatment x region interaction (see Table 5.63 above see below and Table 5.68 below for interaction means and SEM), pairwise comparisons (see Table 5.69 below) revealed treatment effects showing greater positivity for posterior P3 amplitudes following placebo, in comparison to following glucose. Regional effects showed that, following both glucose and placebo, P3 amplitudes were greater at the posterior region, see Figure 5.32 below.

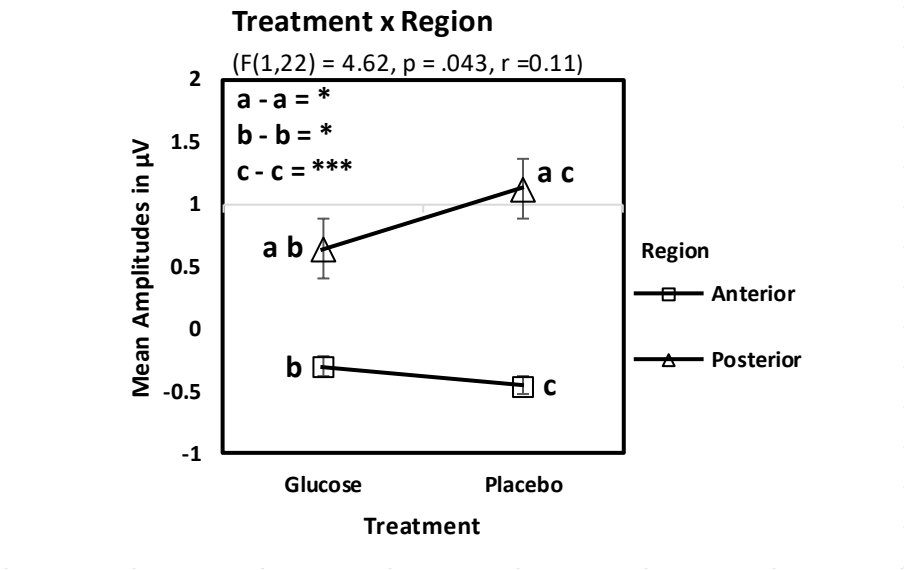
Table 5.68 Encoding Phase P3 Component. Amplitude means and SEMs depicting the treatment x region interaction.

Treatment	Region	Mean	±	SEM
Glucose	Anterior	-0.299	±	0.146
	Posterior	0.644	±	0.18
Placebo	Anterior	-0.453	±	0.143
	Posterior	1.127	±	0.195

Table 5.69 Encoding Phase P3 Component. Significant pairwise comparisons from the Treatment x Region interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition / Group	Pairwise Differences	Mean(SEM)	t(21)=	p Value
Posterior	Placebo > Glucose	Glucose (Mean 0.644, SEM 0.180)	2.808	0.010
		Placebo (Mean 1.127, SEM 0.195)		
Glucose	Posterior > Anterior	Posterior (Mean 0.644, SEM 0.180)	3.052	0.006
		Anterior (Mean -0.299, SEM 0.146)		
Placebo	Posterior > Anterior	Posterior (Mean 1.127, SEM 0.195)	5.302	<0.001
		Anterior (Mean -0.453, SEM 0.143)		

Figure 5.32 P3 component significant pairwise comparisons from the Treatment x Region interaction. Figure key shows pairwise comparisons and significance levels. (p<.05,***<.001).* Bars show standard error.**



The main effect of Treatment (F(1,22) = 5.163, p = .033, r =0.05), see Table 5.63 above, revealed lower P3 amplitudes following glucose (Mean 0.172, SEM 0.055) in comparison to placebo (Mean 0.337, SEM 0.084).

5.6.1.4 Late Positive Component

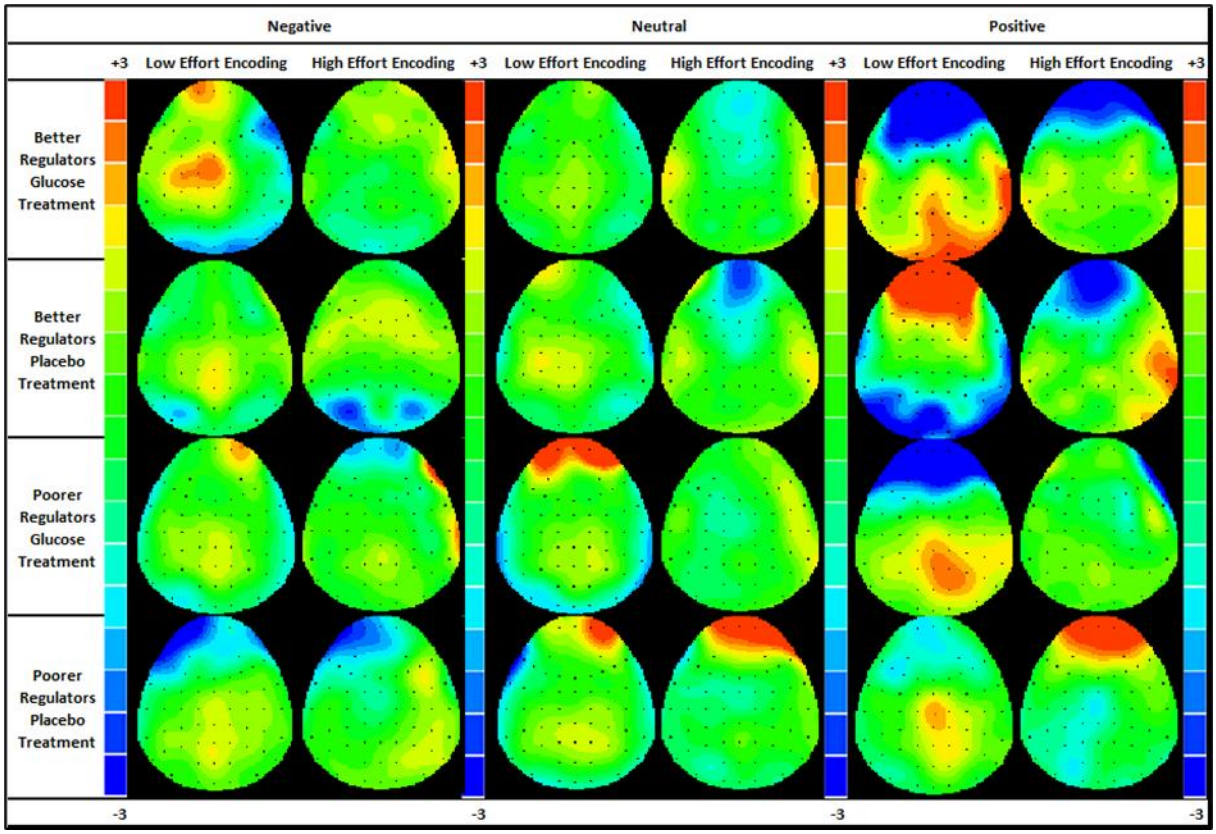
See Appendix 5.10 for the means and SEM for the ERP data for the word recognition encoding phase LPC component analysis. Significant effects and interactions are indicated.

For the analysis of positive going late positive component data for the 540 – 780ms time window the primary six-way glucoregulation x treatment x demand x region x valence x hemisphere was non-significant ($F(1.64,35.97) = 1.118$, $p = .328$, $r = 0.04$). Significant main effects and interactions are shown below in Table 5.70 Only significant higher order interactions are reported in the text. Topographical maps representing the LPC component can be seen in Figure 5.33 below.

Table 5.70 Encoding Phase LPC Component. Significant main effects and interactions from the six-way glucoregulation x treatment x demand x valence x region x hemisphere ANOVA conducted on encoding data in the 540 - 780 ms time window. ANOVA F values, degrees of freedom, significance levels and effect sizes for significant interactions and main effects are shown.

Main Effect/ Interaction	df	F	p value	r
Glucoregulation x Treatment x Demand x Hemisphere	(1.82,40.05)	5.523	0.009	0.06
Treatment x Demand x Hemisphere	(1.82,40.05)	9.512	0.001	0.08
Demand x Hemisphere	(1.54,33.81)	14.103	<.001	0.07
Treatment	(1,22)	9.855	0.005	0.06
Hemisphere	(1.92,42.20)	9.813	<.001	0.06

Figure 5.33 ERP topographies of grand average encoding data for LPC component across the 540-780 ms time window. The colour scale shows amplitude ranges from positive (red) to negative (blue) inflections from +3 to -3 microvolts.



There was a significant four-way glucoregulation x treatment x demand x hemisphere interaction ($F(1.82,40.05) = 5.523$, $p = .009$, $r = 0.06$), see Table 5.70 above and Table 5.71 below for interaction means and SEM). Pairwise comparisons can be seen in Table 5.72 and Figure 5.34 below. Interaction glucoregulation effects showed that following placebo better, compared to poorer regulators, had greater left hemisphere LPC amplitudes during high demand encoding. Also, following placebo poorer, compared to better regulators, had greater right hemisphere LPC amplitudes during high demand encoding. Interaction treatment effects revealed that better regulators had enhanced midline LPC amplitudes during low demand encoding following glucose. Again, for better regulators this treatment pattern was reversed during high demand encoding with midline LPC amplitudes being greater following placebo. Significant pairwise comparisons of the effects of demand and hemisphere on the interaction can be seen in Table 5.72 below.

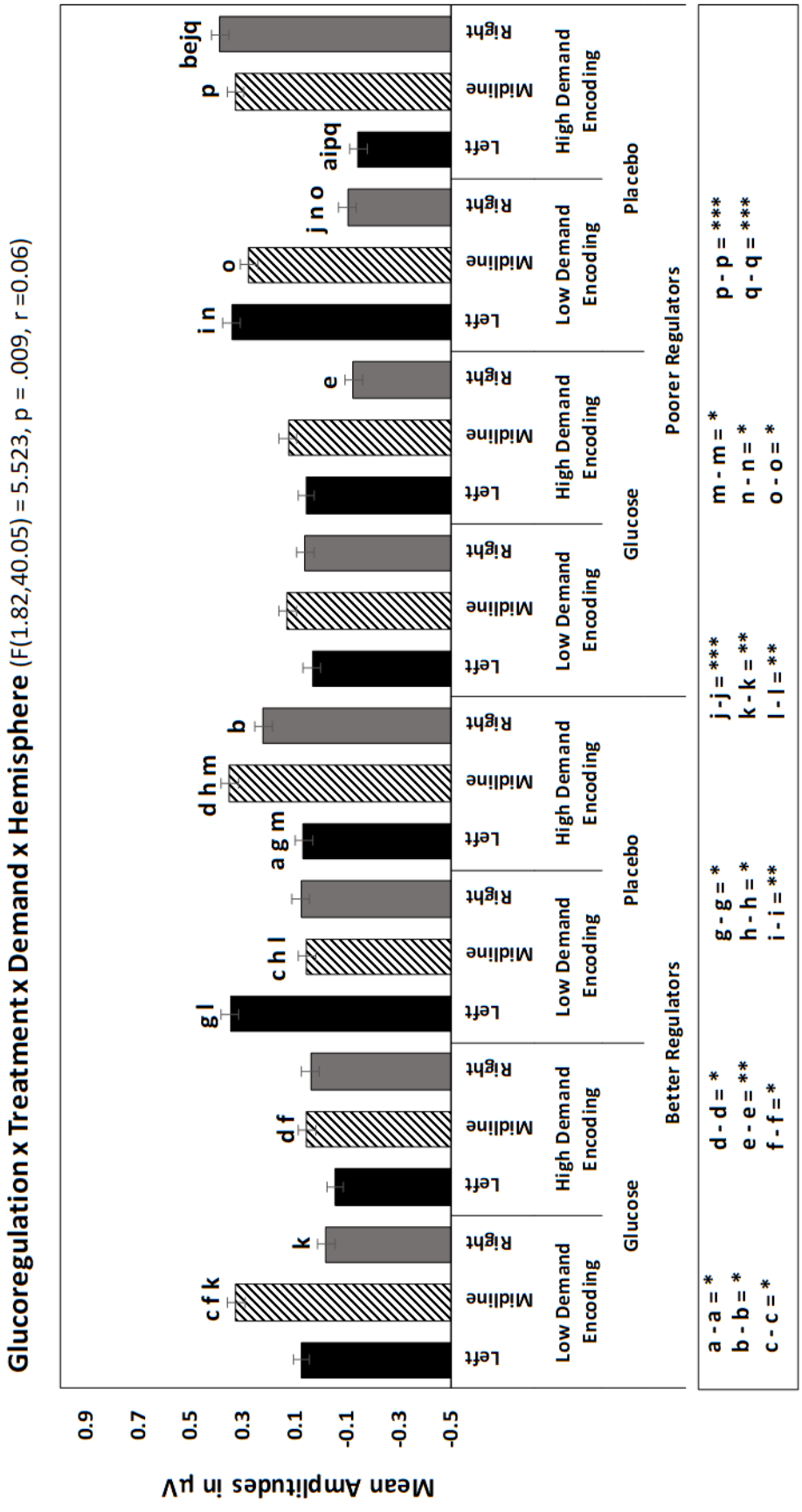
Table 5.71 Encoding Phase LPC Component. Amplitude means and SEMs depicting the glucoregulation x treatment x demand x hemisphere interaction.

Glucoregulation	Treatment	Demand	Hemisphere	Mean	±	SEM
Better Regulators	Glucose	Low Demand Encoding	Left	0.074	±	0.09
			Midline	0.325	±	0.083
			Right	-0.021	±	0.065
		High Demand Encoding	Left	-0.055	±	0.117
			Midline	0.053	±	0.104
			Right	0.038	±	0.111
	Placebo	Low Demand Encoding	Left	0.347	±	0.123
			Midline	0.053	±	0.091
			Right	0.075	±	0.075
		High Demand Encoding	Left	0.066	±	0.069
			Midline	0.35	±	0.103
			Right	0.221	±	0.055
Poorer Regulators	Glucose	Low Demand Encoding	Left	0.033	±	0.09
			Midline	0.127	±	0.083
			Right	0.06	±	0.065
		High Demand Encoding	Left	0.055	±	0.117
			Midline	0.125	±	0.104
			Right	-0.124	±	0.111
	Placebo	Low Demand Encoding	Left	0.34	±	0.123
			Midline	0.276	±	0.091
			Right	-0.102	±	0.075
		High Demand Encoding	Left	-0.143	±	0.069
			Midline	0.327	±	0.103
			Right	0.386	±	0.055

Table 5.72 Encoding Phase LPC Component. Significant pairwise comparisons from the Glucoregulation x Treatment x Demand x Hemisphere interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition / Group	Pairwise Differences	Mean(SEM)	t(21)=	p Value
Placebo, High Demand, Left Hemisphere	Better > Poorer	Better (Mean 0.066, SEM 0.069)	2.133	0.044
		Poorer (Mean -0.143, SEM 0.069)		
Placebo, High Demand, Right Hemisphere	Poorer > Better	Better (Mean 0.221, SEM 0.055)	2.143	0.045
		Poorer (Mean 0.386, SEM 0.055)		
Better Regulators, Low Demand, Midline Hemisphere	Glucose > Placebo	Glucose (Mean 0.325, SEM 0.083)	2.625	0.016
		Placebo (Mean 0.053, SEM 0.091)		
Better Regulators, High Demand, Midline Hemisphere	Placebo > Glucose	Glucose (Mean 0.053, SEM 0.104)	2.129	0.045
		Placebo (Mean 0.350, SEM 0.103)		
Poorer Regulators, High Demand, Right Hemisphere	Placebo > Glucose	Glucose (Mean -0.124, SEM 0.111)	4.359	0.001
		Placebo (Mean 0.386, SEM 0.055)		
Better Regulators, Glucose, Midline Hemisphere	Low > High	Low Demand (Mean 0.325, SEM 0.083)	2.159	0.042
		High Demand (Mean 0.053 SEM 0.104)		
Better Regulators, Placebo, Left Hemisphere	Low > High	Low Demand (Mean 0.347, SEM 0.123)	2.081	0.049
		High Demand (Mean 0.066, SEM 0.069)		
Better Regulators, Placebo, Midline Hemisphere	High > Low	Low Demand (Mean 0.053, SEM 0.091)	2.485	0.021
		High Demand (Mean 0.350, SEM 0.103)		
Poorer Regulators, Placebo, Left Hemisphere	Low > High	Low Demand (Mean 0.340, SEM 0.123)	2.560	0.002
		High Demand (Mean -0.143, SEM 0.069)		
Poorer Regulators, Placebo, Right Hemisphere	High > Low	Low Demand (Mean -0.102, SEM 0.075)	5.083	<0.001
		High Demand (Mean 0.386, SEM 0.055)		
Better Regulators, Glucose, Low Demand	Midline > Right	Right (Mean -0.021, SEM 0.065)	3.977	0.002
		Midline (Mean 0.325, SEM 0.083)		
Better Regulators, Placebo, Low Demand	Left > Midline	Left (Mean 0.347, SEM 0.123)	3.722	0.004
		Midline (Mean 0.053 SEM 0.091)		
Better Regulators, Placebo, High Demand	Midline > Left	Left (Mean 0.066, SEM 0.066)	2.958	0.022
		Midline (Mean 0.350 SEM 0.103)		
Poorer Regulators, Placebo, Low Demand	Left > Right	Left (Mean 0.340, SEM 0.123)	2.986	0.020
		Right (Mean -0.102, SEM 0.075)		
Poorer Regulators, Placebo, Low Demand	Midline > Right	Midline (Mean 0.276, SEM 0.091)	2.953	0.022
		Right (Mean -0.102, SEM 0.075)		
Poorer Regulators, Placebo, High Demand	Midline > Left	Left (Mean -0.143, SEM 0.069)	4.885	<0.001
		Midline (Mean 0.327 SEM 0.103)		
Poorer Regulators, Placebo, High Demand	Right > Left	Right (Mean 0.386, SEM 0.055)	5.750	<0.001
		Left (Mean -0.143, SEM 0.069)		

Figure 5.34 Encoding Phase LPC Component. Significant pairwise comparisons from the Glucoregulation x Treatment x Demand x Hemisphere interaction. See figure key for significance levels (p<.05,**p<.005,***<.001).* Bars show standard error.**



Finally, the main effect of Treatment ($F(1,22) = 9.855$, $p = .005$, $r = 0.06$), see Table 5.70 above, revealed lower LPC amplitudes following glucose (Mean 0.058, SEM 0.035) in comparison to placebo (Mean 0.183, SEM 0.036).

5.6.1.4.1 Summary of Encoding Phase ERP Data Results

P1 component (60-130ms latency range) analysis revealed an interaction between treatment, region, valence, and hemisphere which identified elevated posterior P1 amplitudes for neutral and positive words with a maximal P1 amplitude being elicited at the right posterior by positive words following placebo. P1 amplitudes were greatest across the posterior region. There was also an interaction between glucoregulation, region and hemisphere such that better and poorer regulators had greater posterior P1 amplitudes, but these differed hemispherically, with better regulators having elevated left posterior and poorer regulators with an elevated right posterior P1. Additionally, the interaction between demand, valence and hemisphere identified that low demand during encoding was associated with greater left hemisphere amplitudes being evoked by neutral words compared to positive words. P1 amplitudes were maximal at right hemisphere electrodes.

N1 component (130-220ms latency range) analysis showed a significant interaction between glucoregulation, demand, valence and hemisphere which identified a higher right hemisphere N1 for positive words following high compared to low demand encoding for poorer regulators. Poorer regulators also had greater right hemisphere compared to left hemisphere N1 amplitudes for positive words. There was also a significant interaction between demand, region, valence, and hemisphere which showed that during low demand encoding negative, neutral, and positive words all elicited a higher midline anterior N1 compared to posterior midline amplitudes. This pattern was mixed during high demand encoding but here only for negative and neutral words. Additionally, there was a significant interaction between treatment, region, valence, and hemisphere which showed treatment effects for the anterior but not posterior region. Following glucose, for negative and neutral words there were enhanced right hemisphere anterior N1 amplitudes compared to following placebo. N1 amplitudes were higher at posterior compared to anterior electrodes following both treatments and for all valences. Glucose elicited a greater anterior right hemisphere N1 relative to placebo. The posterior midline N1 was greater than left and right hemisphere amplitudes. The main effect of treatment showed glucose elicited a greater N1 compared to placebo.

P3 component (210-330ms latency range) analysis showed an interaction between demand, region, valence, and hemisphere which revealed a higher anterior P3 during high demand encoding whereas, the posterior P3 was higher during low demand encoding. Neutral words, relative to positive words, evoked enhanced midline and right hemisphere amplitudes during high demand encoding. There was also a significant interaction between treatment, hemisphere and glucoregulation which indicated that poorer regulators had higher right hemisphere P3 amplitudes following placebo relative to glucose. For better regulators there was an enhanced right hemisphere compared to midline P3 following both glucose and placebo treatments. Additionally, the interaction between treatment and region showed that posterior P3 amplitudes were higher following placebo compared to glucose. Following both glucose and placebo posterior P3 amplitudes were greater than anterior amplitudes. The main effect of treatment revealed that P3 amplitudes were lower following glucose.

LPC component (540-780ms latency range) analysis showed a significant interaction between glucoregulation, treatment, demand and hemisphere which indicated that following placebo better regulators had greater left hemisphere LPC amplitudes than did poorer regulators during high demand encoding. Poorer regulators had greater right hemisphere LPC amplitudes during high demand and following placebo than did better regulators. Following glucose and during low demand encoding better regulators had greater midline LPC amplitudes; this was reversed following placebo when better regulators had higher midline LPC amplitudes during high demand encoding. The main effect of treatment showed lower LPC amplitudes following glucose.

5.6.2 Word Recognition

5.6.2.1 FN400 component Old/New Word Analysis

See Appendix 5.11 for the means and SEM for the ERP data for the word recognition phase FN400 component analysis. Significant effects and interactions are indicated.

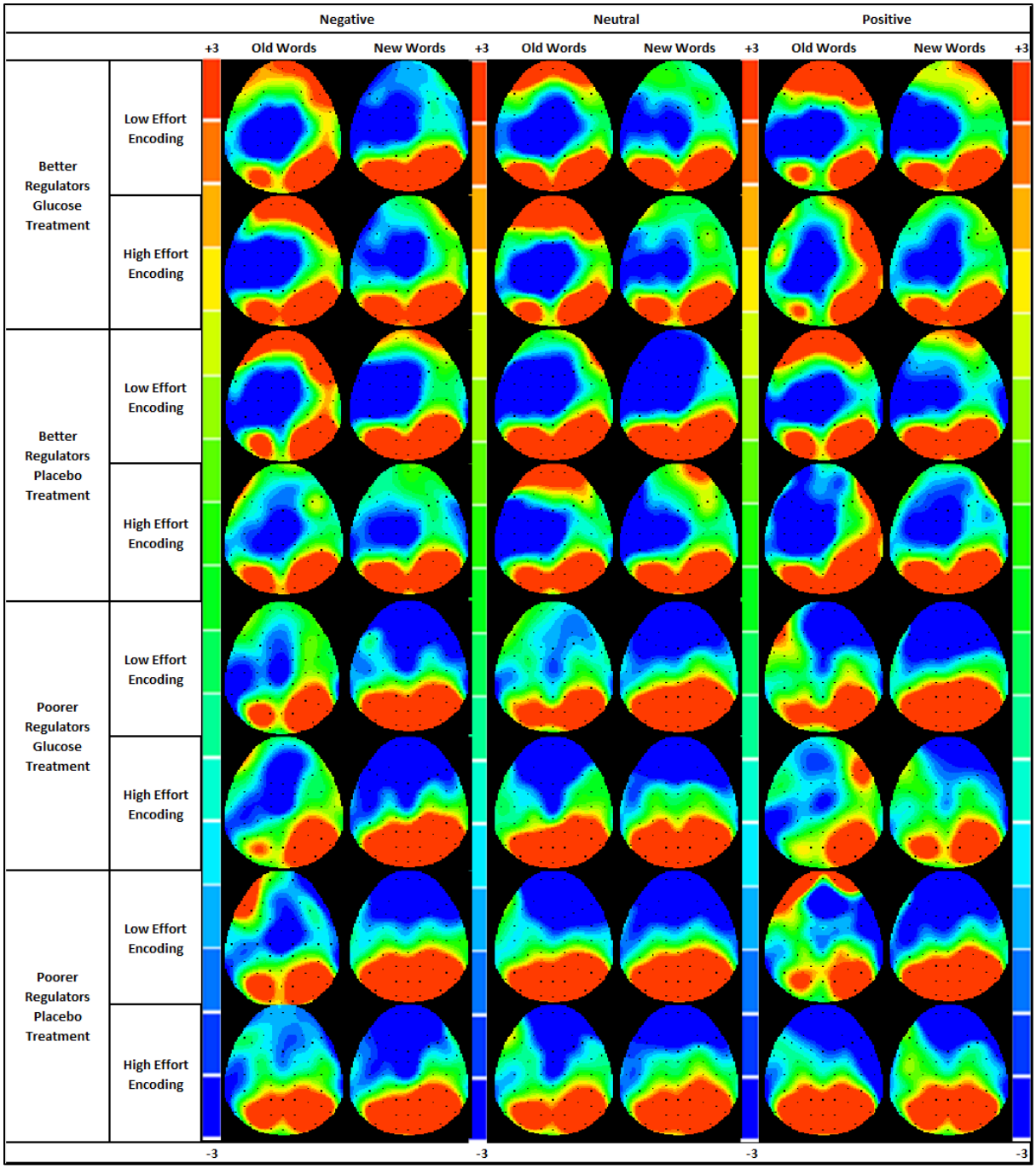
Analysis of the FN400 was conducted on correct recognitions of old words and correct rejections of new words. For the analysis of FN400 component data in the 310 – 480ms time window, the primary seven-way glucoregulation x treatment x word type x demand x region x valence x hemisphere ANOVA was non-significant ($F(4,64.81) = 0.477$, $p = .706$, $r = 0.01$). Significant main effects and

interactions are shown below in Table 5.73. Only significant higher order interactions are reported in the text. Topographical maps representing the FN400 component can be seen in Figure 5.35 below.

Table 5.73 Word Recognition Old/New Correct Recognitions FN400 Component. Significant main effects and interactions from the seven-way glucoregulation x treatment x word type x demand x valence x region x hemisphere ANOVA conducted on recognition data in the 310 - 480 ms time window. ANOVA F values, degrees of freedom, significance levels and effect sizes for significant interactions and main effects are shown.

Main Effect/ Interaction	df	F	p value	r
Glucoregulation x Treatment x Word Type x Valence x Hemisphere	(3.05,67.03)	2.759	0.048	0.02
Glucoregulation x Treatment x Word Type x Hemisphere	(1.58,34.83)	6.773	0.006	0.02
Treatment x Word Type x Hemisphere	(1.58,34.83)	9.051	0.001	0.03
Word Type x Region x Hemisphere	(1.80,39.63)	19.763	<.001	0.04
Word Type x Region	(1,22)	18.801	<.001	0.14
Word Type x Valence	(1.90,41.83)	8.033	0.001	0.03
Region x Hemisphere	(1.71,37.60)	9.913	0.001	0.08
Glucoregulation	(1,22)	4.921	0.037	0.08
Hemisphere	(1.96,43.11)	24.600	<.001	0.17

Figure 5.35 Word Recognition Old/New Correct Recognitions FN400 Component ERP topographies of grand average old/new data for FN400 component across the 310-480 ms time window. The colour scale shows amplitude ranges from positive (red) to negative (blue) inflections from +3 to -3 microvolts.



There was a significant glucoregulation x treatment x word type x valence x hemisphere interaction ($F(3.05,67.03) = 2.759$, $p = .048$, $r = 0.02$), see Table 5.73 above and Table 5.74 below for interaction means and SEM. Pairwise comparisons for interaction effects of glucoregulation, treatment, word type, valence and hemisphere can be seen in Table 5.75 below and Figure 5.36 below. As there were also numerous interaction effects of hemisphere these have not been included in the bar chart but can be seen in the table. The impact of glucoregulation on the interaction showed that following glucose poorer regulators had more positive right hemisphere FN400 amplitudes for negative old words compared to better regulators. Also following glucose, for responses to negative new words poorer regulators had more positive midline hemisphere FN400 amplitudes than did better regulators. Again, following glucose, for positive new words poorer regulators had more positive left hemisphere FN400 amplitudes than did better regulators. Additionally, following glucose, for positive new words poorer regulators had more positive midline hemisphere FN400 amplitudes than did better regulators. Finally, following placebo for new neutral words poorer regulators had more positive midline hemisphere FN400 amplitudes relative to better regulators.

Interaction treatment effects found that following glucose poorer regulators had enhanced amplitudes for right hemisphere old negative words and left hemisphere new positive words. This was reversed for better regulators who had more positive amplitudes following placebo.

Word type interaction effects showed that old negative words elicited greater right hemisphere FN400 amplitudes than did new negative words for poorer regulators following glucose. Conversely, new words had higher FN400 amplitudes than old words following placebo. Valence effects on the interaction revealed a higher left hemisphere FN400 for old neutral words than for old positive words in better regulators post glucose. Additionally, following placebo poorer regulators had enhanced left hemisphere amplitudes for negative words compared to neutral words. The effect of hemisphere on the interaction revealed that FN400 amplitudes were maximal at the right hemisphere electrodes.

Table 5.74 Word Recognition Old/New Correct Recognitions FN400 Component amplitude means and SEMs depicting the glucoregulation x treatment x word type x valence x hemisphere interaction.

Glucoregulation	Treatment	Word_Type	Valence	Hemisphere	Mean	±	SEM
Better Regulators	Glucose	Old Word	Negative	Left	-0.332	±	0.200
				Midline	-0.693	±	0.268
				Right	0.104	±	0.124
			Neutral	Left	-0.382	±	0.176
				Midline	-0.843	±	0.204
				Right	0.197	±	0.111
			Positive	Left	-0.348	±	0.189
				Midline	-0.694	±	0.224
				Right	0.094	±	0.112
		New Word	Negative	Left	-0.481	±	0.154
				Midline	-0.887	±	0.187
				Right	0.098	±	0.131
			Neutral	Left	-0.087	±	0.134
				Midline	-0.787	±	0.153
				Right	0.088	±	0.109
			Positive	Left	-0.47	±	0.131
				Midline	-0.872	±	0.211
				Right	0.248	±	0.133
	Placebo	Old Word	Negative	Left	-0.203	±	0.201
				Midline	-0.765	±	0.250
				Right	0.013	±	0.192
			Neutral	Left	-0.295	±	0.149
				Midline	-0.861	±	0.165
				Right	-0.028	±	0.148
			Positive	Left	-0.22	±	0.194
				Midline	-0.78	±	0.258
				Right	0.099	±	0.229
		New Word	Negative	Left	-0.291	±	0.147
				Midline	-0.966	±	0.222
				Right	0.006	±	0.135
			Neutral	Left	-0.294	±	0.138
				Midline	-0.925	±	0.170
				Right	0.243	±	0.131
			Positive	Left	-0.033	±	0.155
				Midline	-0.599	±	0.208
				Right	0.124	±	0.177
Poorer Regulators	Glucose	Old Word	Negative	Left	-0.033	±	0.200
				Midline	-0.15	±	0.268
				Right	0.534	±	0.124
			Neutral	Left	-0.271	±	0.176
				Midline	-0.419	±	0.204
				Right	0.133	±	0.111
			Positive	Left	-0.153	±	0.189
				Midline	-0.163	±	0.224
				Right	0.3	±	0.112
		New Word	Negative	Left	-0.052	±	0.154
				Midline	-0.337	±	0.187
				Right	0.27	±	0.131
			Neutral	Left	-0.137	±	0.134
				Midline	-0.389	±	0.153
				Right	0.316	±	0.109
			Positive	Left	0.189	±	0.131
				Midline	-0.187	±	0.211
				Right	0.06	±	0.133
	Placebo	Old Word	Negative	Left	0.294	±	0.201
				Midline	-0.358	±	0.250
				Right	0.127	±	0.192
			Neutral	Left	-0.101	±	0.149
				Midline	-0.784	±	0.165
				Right	-0.102	±	0.148
			Positive	Left	0.237	±	0.194
				Midline	-0.336	±	0.258
				Right	0.346	±	0.229
		New Word	Negative	Left	-0.117	±	0.147
				Midline	-0.494	±	0.222
				Right	0.34	±	0.135
			Neutral	Left	-0.176	±	0.138
				Midline	-0.366	±	0.170
				Right	0.437	±	0.131
			Positive	Left	-0.139	±	0.155
				Midline	-0.394	±	0.208
				Right	0.511	±	0.177

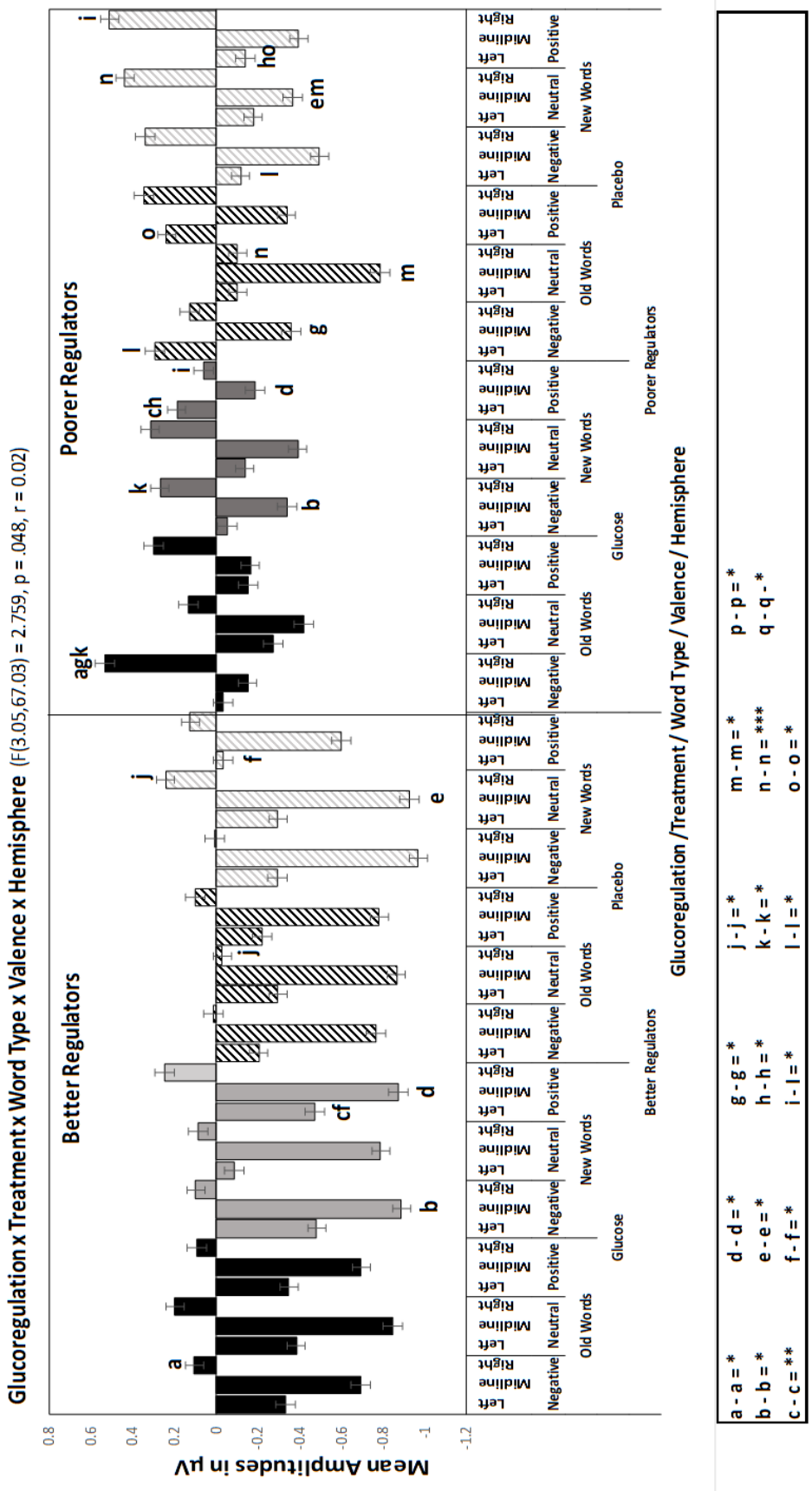
Table 5.75 Word Recognition Old/New Correct Recognitions FN400 Component. Significant pairwise comparisons from the Glucoregulation x Treatment x Word Type x Valence x Hemisphere interaction. Pairwise differences, means and SEMs, t-values,

Condition / Group	Pairwise Differences	Mean(SEM)	t(21)=	p Value
Glucose, Old Words, Negative, Right Hemisphere	Poorer more positive than better	Better (Mean 0.104, SEM 0.124)	2.457	0.022
		Poorer (Mean 0.534, SEM 0.124)		
Glucose, New Words, Negative, Midline Hemisphere	Poorer more positive than better	Better (Mean -0.887, SEM 0.187)	2.083	0.049
		Poorer (Mean -0.337, SEM 0.055)		
Glucose, New Words, Positive, Left Hemisphere	Poorer more positive than better	Better (Mean -0.470, SEM 0.131)	3.557	0.002
		Poorer (Mean 0.189, SEM 0.131)		
Glucose, New Words, Positive, Midline Hemisphere	Poorer more positive than better	Better (Mean -0.872, SEM 0.211)	2.291	0.032
		Poorer (Mean -0.187, SEM 0.211)		
Placebo, New Words, Neutral, Midline Hemisphere	Poorer more positive than better	Better (Mean -0.925, SEM 0.170)	2.320	0.030
		Poorer (Mean -0.366, SEM 0.170)		
Better Regulators, New Words, Positive, Left Hemisphere	Placebo more positive than Glucose	Glucose (Mean -0.481, SEM 0.154)	2.813	0.010
		Placebo (Mean -0.291, SEM 0.147)		
Poorer Regulators, Old Words, Negative, Right Hemisphere	Glucose more positive than Placebo	Glucose (Mean 0.534, SEM 0.124)	2.299	0.031
		Placebo (Mean 0.127, SEM 0.192)		
Poorer Regulators, New Words, Positive, Left Hemisphere	Glucose more positive than Placebo	Glucose (Mean 0.189, SEM 0.131)	2.110	0.046
		Placebo (Mean -0.139, SEM 0.155)		
Poorer Regulators, New Words, Positive, Right Hemisphere	Placebo more positive than Glucose	Glucose (Mean 0.060, SEM 0.133)	2.750	0.012
		Placebo (Mean 0.511, SEM 0.177)		
Better Regulators, Placebo, Neutral, Right Hemisphere	New Words more positive than Old Words	Old Words (Mean -0.028, SEM 0.148)	2.185	0.040
		New Words (Mean 0.243, SEM 0.131)		
Poorer Regulators, Glucose, Negative, Right Hemisphere	Old Words more positive than New Words	Old Words (Mean 0.534, SEM 0.124)	2.146	0.043
		New Words (Mean 0.270, SEM 0.131)		
Poorer Regulators, Placebo, Negative, Left Hemisphere	New Words more positive than Old Words	Old Words (Mean 0.294, SEM 0.201)	2.146	0.044
		New Words (Mean -0.117, SEM 0.147)		
Poorer Regulators, Placebo, Neutral, Midline Hemisphere	New Words more positive than Old Words	Old Words (Mean -0.784, SEM 0.165)	2.703	0.013
		New Words (Mean -0.366, SEM 0.170)		
Poorer Regulators, Placebo, Neutral, Right Hemisphere	New Words more positive than Old Words	Old Words (Mean -0.102, SEM 0.165)	4.339	<0.001
		New Words (Mean 0.437, SEM 0.131)		
Poorer Regulators, Placebo, Positive, Left Hemisphere	Old Words more positive than New Words	Old Words (Mean 0.237, SEM 0.194)	3.008	0.007
		New Words (Mean -0.139, SEM 0.155)		
Better Regulators, Glucose, New Words, Left Hemisphere	Neutral Words more positive than Positive Words	Neutral (Mean -0.087, SEM 0.134)	2.653	0.022
		Positive (Mean -0.470, SEM 0.131)		
Poorer Regulators, Placebo, Old Words, Left Hemisphere	Negative Words more positive than Neutral Words	Neutral (Mean -0.101, SEM 0.149)	2.623	0.048
		Negative (Mean 0.294, SEM 0.120)		

Continued.

Condition / Group	Pairwise Differences	Mean(SEM)	t(21)=	p Value
Better Regulators, Glucose, Old Words, Negative	Right Hemisphere more positive than Midline	Right (Mean 0.104, SEM 0.124) Midline (Mean -0.693, SEM 0.268)	3.113	0.015
Better Regulators, Glucose, Old Words, Neutral	Left Hemisphere more positive than Midline	Left (Mean -0.382, SEM 0.176) Midline (Mean -0.843, SEM 0.204)	2.659	0.042
Better Regulators, Glucose, Old Words, Neutral	Right Hemisphere more positive than Midline	Right (Mean 0.197, SEM 0.111) Midline (Mean -0.843, SEM 0.204)	5.445	<0.001
Better Regulators, Glucose, Old Words, Positive	Right Hemisphere more positive than Midline	Right (Mean 0.094, SEM 0.112) Midline (Mean -0.694, SEM 0.112)	4.169	0.001
Better Regulators, Glucose, New Words, Negative	Left Hemisphere more positive than Midline	Left (Mean -0.481, SEM 0.154) Midline (Mean -0.887, SEM 0.187)	2.707	0.038
Better Regulators, Glucose, New Words, Negative	Right Hemisphere more positive than Midline	Right (Mean 0.098, SEM 0.187) Midline (Mean -0.887, SEM 0.187)	4.945	<0.001
Better Regulators, Glucose, New Words, Neutral	Left Hemisphere more positive than Midline	Left (Mean -0.087, SEM 0.134) Midline (Mean -0.787, SEM 0.153)	4.516	0.001
Better Regulators, Glucose, New Words, Neutral	Right Hemisphere more positive than Midline	Right (Mean 0.088, SEM 0.109) Midline (Mean -0.787, SEM 0.153)	5.503	<0.001
Better Regulators, Glucose, New Words, Positive	Right Hemisphere more positive than Left	Left (Mean -0.470, SEM 0.131) Right (Mean 0.248, SEM 0.133)	3.447	0.007
Better Regulators, Glucose, New Words, Positive	Right Hemisphere more positive than Midline	Right (Mean 0.248, SEM 0.133) Midline (Mean -0.872, SEM 0.133)	5.490	<0.001
Better Regulators, Placebo, Old Words, Negative	Right Hemisphere more positive than Midline	Right (Mean 0.013, SEM 0.192) Midline (Mean -0.765, SEM 0.250)	3.412	0.008
Better Regulators, Placebo, Old Words, Neutral	Right Hemisphere more positive than Midline	Right (Mean -0.028, SEM 0.148) Midline (Mean -0.861, SEM 0.165)	4.706	<0.001
Better Regulators, Placebo, Old Words, Positive	Right Hemisphere more positive than Midline	Right (Mean 0.099, SEM 0.229) Midline (Mean -0.780, SEM 0.258)	2.911	0.024
Better Regulators, Placebo, New Words, Negative	Left Hemisphere more positive than Midline	Left (Mean -0.291, SEM 0.147) Midline (Mean -0.966, SEM 0.222)	3.689	0.004
Better Regulators, Placebo, New Words, Negative	Right Hemisphere more positive than Midline	Right (Mean 0.006, SEM 0.135) Midline (Mean -0.966, SEM 0.222)	4.884	<.001
Better Regulators, Placebo, New Words, Neutral	Left Hemisphere more positive than Midline	Left (Mean -0.294, SEM 0.138) Midline (Mean -0.925, SEM 0.170)	3.525	0.006
Better Regulators, Placebo, New Words, Neutral	Right Hemisphere more positive than Midline	Right (Mean 0.243, SEM 0.131) Midline (Mean -0.925, SEM 0.170)	5.309	<0.001
Better Regulators, Placebo, New Words, Positive	Left Hemisphere more positive than Midline	Left (Mean -0.033, SEM 0.155) Midline (Mean -0.599, SEM 0.208)	2.608	0.048
Better Regulators, Placebo, New Words, Positive	Right Hemisphere more positive than Midline	Right (Mean 0.124, SEM 0.177) Midline (Mean -0.599, SEM 0.208)	3.431	0.007
Poorer Regulators, Glucose, Old Words, Negative	Right Hemisphere more positive than Midline	Right (Mean 0.534, SEM 0.124) Midline (Mean -0.150, SEM 0.268)	2.672	0.041
Poorer Regulators, Glucose, Old Words, Neutral	Right Hemisphere more positive than Midline	Right (Mean 0.133, SEM 0.111) Midline (Mean -0.419, SEM 0.204)	2.890	0.025
Poorer Regulators, Glucose,New Words, Negative	Right Hemisphere more positive than Midline	Right (Mean 0.270, SEM 0.131) Midline (Mean -0.337, SEM 0.187)	3.050	0.017
Poorer Regulators, Glucose, New Words, Neutral	Right Hemisphere more positive than Midline	Right (Mean 0.316, SEM 0.109) Midline (Mean -0.389, SEM 0.153)	4.434	0.001
Poorer Regulators, Glucose, New Words, Neutral	Left Hemisphere more positive than Midline	Left (Mean -0.137, SEM 0.134) Midline (Mean -0.389, SEM 0.153)	3.859	0.003
Poorer Regulators, Placebo, New Words, Negative	Right Hemisphere more positive than Left	Right (Mean 0.437, SEM 0.131) Left (Mean -0.176, SEM 0.138)	2.799	0.031
Poorer Regulators, Placebo, New Words, Negative	Right Hemisphere more positive than Midline	Right (Mean 0.437, SEM 0.131) Midline (Mean -0.366, SEM 0.170)	3.645	0.004
Poorer Regulators, Placebo, New Words, Positive	Right Hemisphere more positive than Left	Right (Mean 0.511, SEM 0.177) Left (Mean -0.139, SEM 0.155)	2.863	0.027
Poorer Regulators, Placebo, New Words, Positive	Right Hemisphere more positive than Midline	Right (Mean 0.511, SEM 0.177) Midline (Mean -0.394, SEM 0.208)	4.289	0.001

Figure 5.36 Word Recognition Old/New Correct Recognitions FN400 Component. Pairwise comparisons from glucoregulation x treatment x word type x valence x hemisphere interaction showing interaction effects of glucoregulation, treatment, word type and valence. For significance levels see figure key *(*p<.05, **p<.005,*p<.001).* . Bars show standard error.**



For the word type x region x hemisphere interaction (F(1.80,39.63) =19.763, p = .006, r =0.04) (see Table 5.73 above and Table 5.76 below for interaction means and SEM). Significant pairwise comparisons from the interaction can be seen below in Table 5.77 and Figure 5.37. Interaction effects of word type showed old words elicited higher FN400 than new words in the anterior region, but higher amplitudes were seen for new words relative to old words in the posterior region. Hemisphere effects showed higher right hemisphere FN400 amplitudes for old and new words and both regions. Interaction effects of region did not yield any significant pairwise comparisons.

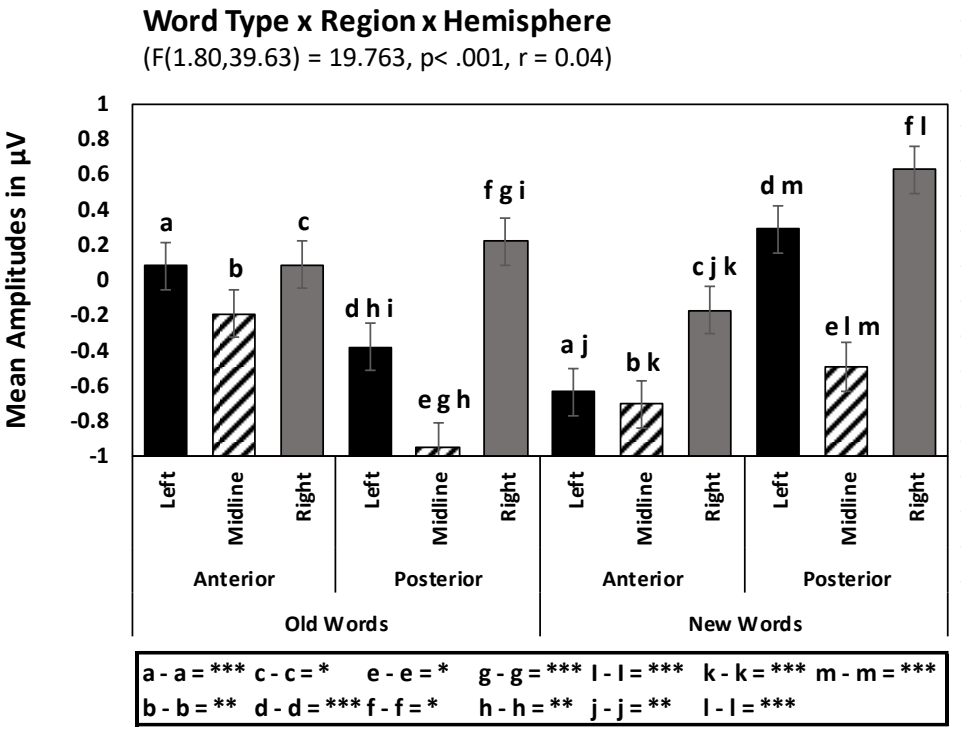
Table 5.76 Word Recognition Old/New Correct Recognitions FN400 Component. Amplitude means and SEMs depicting the word type x region x hemisphere interaction.

Word Type	Valence	Hemisphere	Mean	±	SEM
Old Words	Anterior	Left	0.079	±	0.265
		Midline	-0.192	±	0.239
		Right	0.084	±	0.200
	Posterior	Left	-0.38	±	0.245
		Midline	-0.95	±	0.303
		Right	0.219	±	0.276
New Words	Anterior	Left	-0.637	±	0.252
		Midline	-0.706	±	0.237
		Right	-0.171	±	0.201
	Posterior	Left	0.289	±	0.252
		Midline	-0.494	±	0.284
		Right	0.628	±	0.277

Table 5.77 Word Recognition Old/New Correct Recognitions FN400 Component. Significant pairwise comparisons from the Word Type x Region x Hemisphere interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

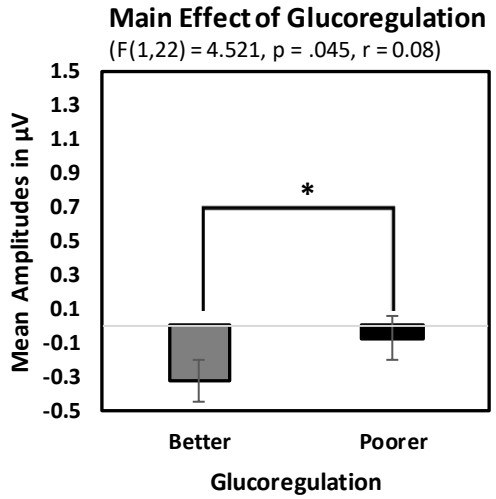
Condition / Group	Pairwise Differences	Mean(SEM)	t(22)=	p Value
Anterior Region, Left Hemisphere	Old Words more positive than New Words	Old Words (Mean 0.079, SEM 0.265)	5.226	<0.001
		New Words (Mean -0.637, SEM 0.252)		
Anterior Region, Midline Hemisphere	Old Words more positive than New Words	Old Words (Mean -0.192, SEM 0.239)	3.894	0.001
		New Words (Mean -0.706, SEM 0.237)		
Anterior Region, Right Hemisphere	Old Words more positive than New Words	Old Words (Mean 0.084, SEM 0.200)	2.179	0.041
		New Words (Mean -0.171, SEM 0.201)		
Posterior Region, Left Hemisphere	New Words more positive than Old Words	Old Words (Mean -0.380, SEM 0.245)	5.107	<0.001
		New Words (Mean 0.289, SEM 0.252)		
Posterior Region, Midline Hemisphere	New Words more positive than Old Words	Old Words (Mean -0.950, SEM 0.303)	2.407	0.025
		New Words (Mean -0.494, SEM 0.284)		
Posterior Region, Right Hemisphere	New Words more positive than Old Words	Old Words (Mean 0.219, SEM 0.276)	3.098	0.005
		New Words (Mean 0.628, SEM 0.277)		
Old Words, Posterior Region	Right Hemisphere more positive than Midline Left Hemisphere more positive than Midline	Right (Mean 0.219, SEM 0.276)	6.718	<0.001
		Midline (Mean -0.950, SEM 0.303)		
Old Words, Posterior Region		Left (Mean -0.380, SEM 0.245)	3.647	0.004
		Midline (Mean -0.950, SEM 0.303)		
Old Words, Posterior Region	Right Hemisphere more positive than Midline	Right (Mean 0.219, SEM 0.276)	5.226	<0.001
		Left (Mean -0.380, SEM 0.245)		
New Words, Anterior Region	Right Hemisphere more positive than Midline Left Hemisphere more positive than Midline	Right (Mean -0.171, SEM 0.201)	3.851	0.003
		Left (Mean -0.380, SEM 0.245)		
New Words, Anterior Region		Right (Mean -0.171, SEM 0.201)	5.194	<0.001
		Midline (Mean -0.706, SEM 0.237)		
New Words, Posterior Region	Right Hemisphere more positive than Midline Left Hemisphere more positive than Midline	Right (Mean 0.628, SEM 0.277)	6.165	<0.001
		Midline (Mean -0.494, SEM 0.284)		
New Words, Posterior Region		Left (Mean 0.289, SEM 0.252)	4.810	<0.001
		Midline (Mean -0.494, SEM 0.284)		

Figure 5.37 Word Recognition Old/New Correct Recognitions FN400 Component. Significant pairwise comparisons from the Word Type x Region x Hemisphere interaction. Figure key shows pairwise comparisons and significance levels. *(*p<.05,p<.005,***p<.001)*. Bars show standard error.**



Finally, the main effect of glucoregulation (F(1,22) =4.921, p = .037, r =0.08) (see Figure 5.38 below) showed that poorer regulators had higher FN400 amplitudes (Mean -0.075, SEM 0.085) than did better regulators (Mean -0.329, SEM 0.085).

Figure 5.38 Word Recognition Old/New Correct Recognitions FN400 Component. Main effect of glucoregulation *(*p <.05)* . Bars show standard error.



5.6.2.2 Late posterior component Old/New Words

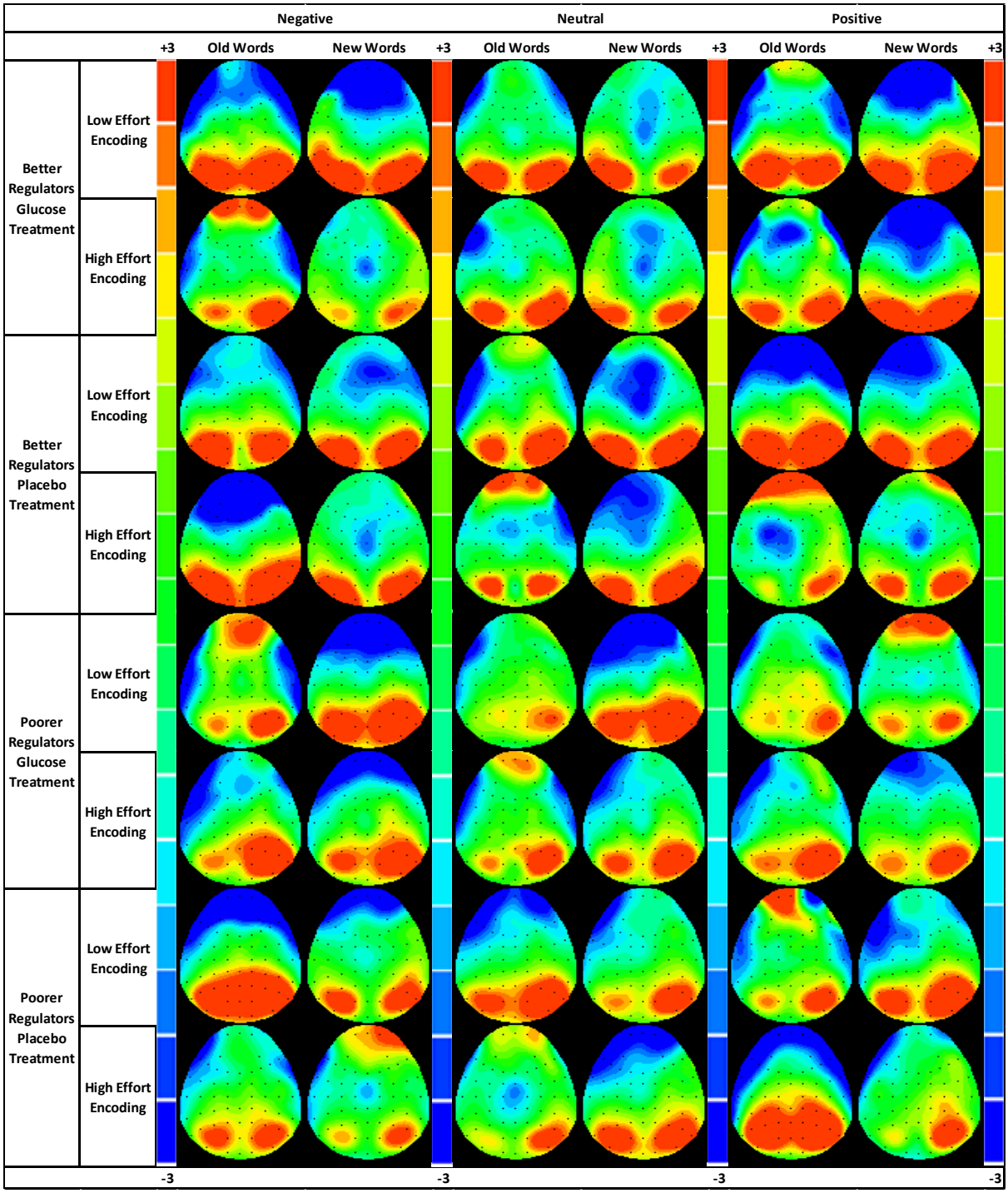
See Appendix 5.12 for the means and SEM for the ERP data for the word recognition phase LPC component analysis. Significant effects and interactions are indicated.

Analysis of the LPC was conducted on correct recognitions of old words and correct rejections of new words. For the analysis of LPC component data in the 470 – 780ms time window, the primary seven-way glucoregulation x treatment x word type x demand x region x valence x hemisphere ANOVA was non-significant (F (2.24,49.32)= 1.034, p = .370, r = 0.01). Significant interactions are shown below in Table 5.78. Only significant higher order interactions are reported in the text. Topographical maps representing the FN400 component can be seen in Figure 5.39 below.

Table 5.78 Word Recognition Old/New Correct Recognitions LPC Component. Significant main effects and interactions from the seven-way glucoregulation x treatment x word type x demand x region x valence x hemisphere mixed factorial ANOVA conducted on recognition data in the 470 - 780 ms time window. ANOVA F values, degrees of freedom, significance levels and effect sizes for significant interactions and main effects are shown.

Main Effect/ Interaction	df	F	p value	r
Glucoregulation x Treatment x Word Type x Valence x Hemisphere	(3.05,67.15)	3.089	0.032	0.02
Glucoregulation x Word Type x Valence x Hemisphere	(3.04,66.94)	2.863	0.043	0.02
Glucoregulation x Treatment x Valence x Hemisphere	(3.02,66.46)	3.069	0.033	0.02
Treatment x Word Type x Region x Hemisphere	(1.80,39.53)	3.881	0.033	0.01
Word Type x Region x Hemisphere	(1.59,35.01)	9.964	0.001	0.02
Demand x Region	(1,22)	4.59	0.043	0.04
Word Type x Region	(1,22)	6.389	0.019	0.10
Word Type x Demand	(1,22)	5.246	0.032	0.02
Glucoregulation x Hemisphere	(1.75,34.45)	4.269	0.025	0.05
Hemisphere	(1.75,34.45)	8.402	0.001	0.06
Region	(1,22)	20.43	<0.001	0.50
Demand	(1,22)	8.869	0.007	0.02
Word Type	(1,22)	5.056	0.035	0.03

Figure 5.39 Word Recognition Old/New Correct Recognitions LPC Component. ERP topographies of grand average old/new data for LPC component across the 470-780 ms time window. The colour scale shows amplitude ranges from positive (red) to negative (blue) inflections from +3 to -3 microvolts.



For the glucoregulation x treatment x word type x valence x hemisphere interaction ($F(3.05,67.15) = 3.089$, $p = .032$, $r = 0.02$), see Table 5.78 above and Table 5.79 below for interaction means and SEM. Pairwise comparisons for interaction effects of glucoregulation, treatment, word type, valence and hemisphere can be seen in Table 5.80 below and Figure 5.40 below. As there were numerous interaction effects of hemisphere these have not been included in the bar chart but can be seen in the table.

Glucoregulation effects on the interaction showed poorer regulators had greater LPC amplitudes than better regulators following glucose for old, neutral words at right hemisphere, also for new, negative words at midline, for new, neutral at both midline and right hemisphere. Similarly, poorer regulators had greater amplitudes for old, negative words at right hemisphere electrodes than did better regulators following placebo.

Interaction treatment effects revealed that following placebo, better regulators had higher right hemisphere LPC in response to new neutral words relative to glucose. This was reversed for poorer regulators who had higher right hemisphere LPC in response to new neutral words following glucose relative to placebo.

Effects of word type on the interaction revealed that following glucose, better regulators responses to neutral words elicited higher midline LPC amplitudes for new words compared to old words. Also, following placebo poorer regulators responses to negative words elicited higher right hemisphere LPC amplitudes for new words compared to old words. Differentially, that following placebo, poorer regulators responses to positive words elicited higher left hemisphere LPC amplitudes for old words compared to new words. There were no significant effects of valence on the interaction.

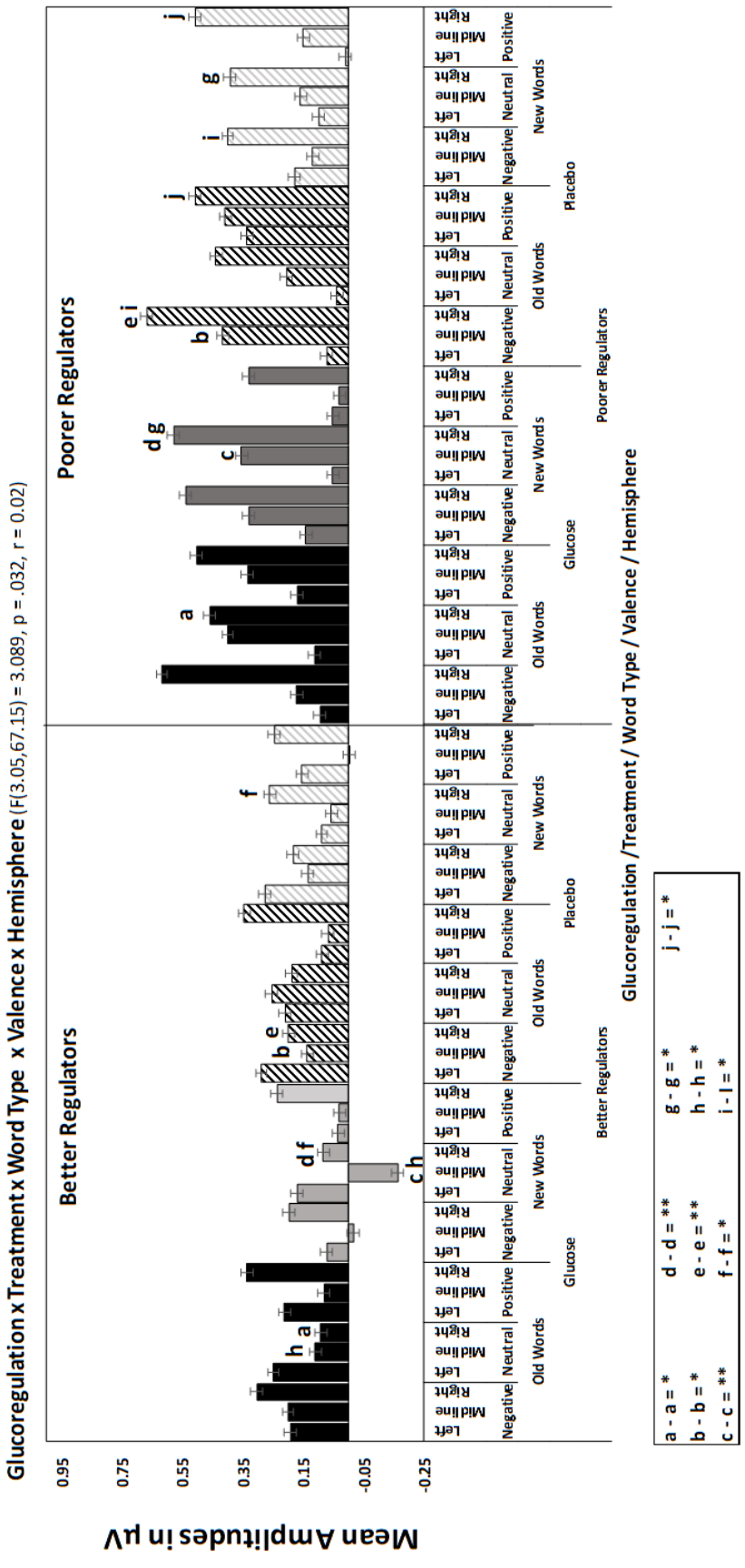
Table 5.79 Word Recognition Old/New Correct Recognitions LPC Component. Amplitude means and SEMs depicting the glucoregulation x treatment x word type x valence x hemisphere interaction.

Glucoregulation	Treatment	Word_Type	Valence	Hemisphere	Mean	±	SEM
Better Regulators	Glucose	Old Word	Negative	Left	0.193	±	0.119
				Midline	0.2	±	0.127
				Right	0.303	±	0.120
			Neutral	Left	0.249	±	0.109
				Midline	0.109	±	0.121
				Right	0.093	±	0.110
			Positive	Left	0.212	±	0.103
				Midline	0.082	±	0.129
				Right	0.336	±	0.132
		New Word	Negative	Left	0.073	±	0.126
				Midline	-0.017	±	0.112
				Right	0.196	±	0.118
			Neutral	Left	0.17	±	0.087
				Midline	-0.164	±	0.112
				Right	0.083	±	0.102
			Positive	Left	0.034	±	0.089
				Midline	0.03	±	0.134
				Right	0.237	±	0.114
	Placebo	Old Word	Negative	Left	0.289	±	0.129
				Midline	0.136	±	0.172
				Right	0.198	±	0.101
			Neutral	Left	0.211	±	0.115
				Midline	0.254	±	0.096
				Right	0.188	±	0.087
			Positive	Left	0.088	±	0.115
				Midline	0.068	±	0.128
				Right	0.345	±	0.083
		New Word	Negative	Left	0.277	±	0.081
				Midline	0.135	±	0.111
				Right	0.184	±	0.092
			Neutral	Left	0.089	±	0.076
				Midline	0.056	±	0.091
				Right	0.262	±	0.096
			Positive	Left	0.155	±	0.095
				Midline	-0.002	±	0.142
				Right	0.245	±	0.114
Poorer Regulators	Glucose	Old Word	Negative	Left	0.095	±	0.119
				Midline	0.172	±	0.127
				Right	0.618	±	0.120
			Neutral	Left	0.113	±	0.109
				Midline	0.4	±	0.121
				Right	0.46	±	0.110
			Positive	Left	0.171	±	0.103
				Midline	0.335	±	0.129
				Right	0.504	±	0.132
		New Word	Negative	Left	0.142	±	0.126
				Midline	0.331	±	0.112
				Right	0.54	±	0.118
			Neutral	Left	0.053	±	0.087
				Midline	0.354	±	0.112
				Right	0.58	±	0.102
			Positive	Left	0.053	±	0.089
				Midline	0.03	±	0.134
				Right	0.331	±	0.114
	Placebo	Old Word	Negative	Left	0.073	±	0.129
				Midline	0.417	±	0.172
				Right	0.669	±	0.101
			Neutral	Left	0.039	±	0.115
				Midline	0.205	±	0.096
				Right	0.439	±	0.087
			Positive	Left	0.336	±	0.115
				Midline	0.408	±	0.128
				Right	0.508	±	0.083
		New Word	Negative	Left	0.179	±	0.081
				Midline	0.119	±	0.111
				Right	0.4	±	0.092
			Neutral	Left	0.1	±	0.076
				Midline	0.159	±	0.091
				Right	0.393	±	0.096
			Positive	Left	0.011	±	0.095
				Midline	0.149	±	0.142
				Right	0.508	±	0.114

Table 5.80 Word Recognition Old/New Correct Recognitions LPC Component. Significant pairwise comparisons from the Glucoregulation x Treatment x Word Type x Valence x Hemisphere interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition / Group	Pairwise Differences	Mean(SEM)	t(21)=	p Value
Glucose, Old Words, Neutral, Right Hemisphere	Poorer more positive than better	Better (Mean 0.093, SEM 0.110)	2.353	0.028
		Poorer (Mean 0.460, SEM 0.110)		
Glucose, New Words, Negative, Midline Hemisphere	Poorer more positive than better	Better (Mean -0.017, SEM 0.187)	2.182	0.040
		Poorer (Mean 0.331, SEM 0.112)		
Glucose, New Words, Neutral, Midline Hemisphere	Poorer more positive than better	Better (Mean -0.164, SEM 0.112)	3.278	0.003
		Poorer (Mean 0.354, SEM 0.112)		
Glucose, New Words, Neutral, Right Hemisphere	Poorer more positive than better	Better (Mean 0.083, SEM 0.102)	3.451	0.002
		Poorer (Mean 0.580, SEM 0.102)		
Placebo, Old Words, Negative,Right Hemisphere	Poorer more positive than better	Better (Mean 0.198, SEM 0.101)	3.294	0.003
		Poorer (Mean 0.669, SEM 0.101)		
Better Regulators, New Words, Neutral, Right Hemisphere	Placebo more positive than Glucose	Glucose (Mean 0.083, SEM 0.102)	2.571	0.018
		Placebo (Mean 0.262, SEM 0.102)		
Poorer Regulators, New Words, Neutral, Right Hemisphere	Glucose more positive than Placebo	Glucose (Mean 0.580, SEM 0.102)	2.671	0.014
		Placebo (Mean 0.393, SEM 0.096)		
Better Regulators, Glucose, Neutral, Midline Hemisphere	New Words more positive than Old Words	Old Words (Mean 0.109, SEM 0.121)	2.528	0.019
		New Words (Mean -0.164, SEM 0.112)		
Poorer Regulators, Placebo, Negative, Right Hemisphere	New Words more positive than Old Words	Old Words (Mean 0.669, SEM 0.101)	2.924	0.008
		New Words (Mean 0.400, SEM 0.092)		
Poorer Regulators, Placebo, Positive, Left Hemisphere	Old Words more positive than New Words	Old Words (Mean 0.336, SEM 0.115)	2.418	0.024
		New Words (Mean 0.011, SEM 0.0955)		
Better Regulators, Glucose, New Words, Neutral	Left Hemisphere more positive than Midline	Left (Mean 0.170, SEM 0.087)	2.630	0.045
		Midline (Mean -0.164, SEM 0.112)		
Poorerer Regulators, Glucose, Old Words, Negative	Right Hemisphere more positive than Left	Left (Mean 0.095, SEM 0.119)	2.682	0.041
		Right (Mean 0.618, SEM 0.120)		
Poorer Regulators, Glucose, Old Words, Neutral	Midline Hemisphere more positive than Left	Left (Mean 0.113, SEM 0.109)	2.899	0.026
		Midline (Mean 0.400, SEM 0.121)		
Poorer Regulators, Glucose, New Words, Negative	Right Hemisphere more positive than Left	Left (Mean 0.142, SEM 0.126)	2.823	0.030
		Right (Mean 0.540, SEM 0.118)		
Poorer Regulators, Glucose, New Words, Neutral	Right Hemisphere more positive than Left	Left (Mean 0.053, SEM 0.087)	3.513	0.006
		Right (Mean 0.580, SEM 0.087)		
Poorer Regulators, Glucose, New Words, Positive	Right Hemisphere more positive than Midline	Right (Mean 0.331, SEM 0.114)	3.202	0.012
		Midline (Mean 0.030, SEM 0.134)		
Poorer Regulators, Placebo, Old Words, Negative	Right Hemisphere more positive than Left	Left (Mean 0.073, SEM 0.129)	3.548	0.005
		Right (Mean 0.669, SEM 0.101)		
Poorer Regulators, Placebo, Old Words, Negative	Midline Hemisphere more positive than Left	Left (Mean 0.073, SEM 0.129)	2.722	0.036
		Midline (Mean 0.417, SEM 0.172)		
Poorer Regulators, Placebo, Old Words, Neutral	Right Hemisphere more positive than Left	Left (Mean 0.039, SEM 0.115)	2.649	0.044
		Right (Mean 0.439, SEM 0.087)		
Poorer Regulators, Placebo, New Words, Positive	Right Hemisphere more positive than Left	Left (Mean 0.011, SEM 0.095)	3.307	0.010
		Right (Mean 0.508, SEM 0.114)		

Figure 5.40 Word Recognition Old/New Correct Recognitions LPC Component. Pairwise comparisons from the glucoregulation x treatment x word type x valence x hemisphere interaction showing interaction effects of glucoregulation, treatment, word type and valence. For significance levels see figure key *(*p<.05, **p<.005,*p<.001).* Bars show standard error.**



For the treatment x word type x region x hemisphere interaction ($F(1.80,39.53) = 3.881$, $p = .033$, $r = 0.01$), see Table 5.78 above and Table 5.81 below for interaction means and SEM. There were no effects of treatment on the interaction; pairwise comparisons for interaction effects of word type, region and hemisphere can be seen in Table 5.82 below and Figure 5.41 below.

For word type interaction effects, pairwise comparisons show that compared to new words, old words had higher posterior LPC amplitudes at both left and midline electrodes following glucose. Also, compared to old words, new words had higher anterior left hemisphere LPC amplitudes following placebo. Additionally compared to new words, old words had higher posterior LPC amplitudes at both left and midline electrodes following placebo. This follows the expected pattern of old recollected words having more positive posterior LPC amplitudes and new unseen words having more negative going anterior LPC amplitudes.

Regional effects on the interaction show that posterior LPC amplitudes were greater than anterior across all conditions which is commensurate with the view that the posterior LPC indexes more explicit recollection (Curran, 2000; Rugg & Curran, 2007).

Interaction hemisphere effects revealed greater right compared to midline hemisphere posterior LPC amplitudes following both glucose and placebo for new words. Also, a greater right compared to left hemisphere anterior LPC amplitudes following both glucose and placebo for old words.

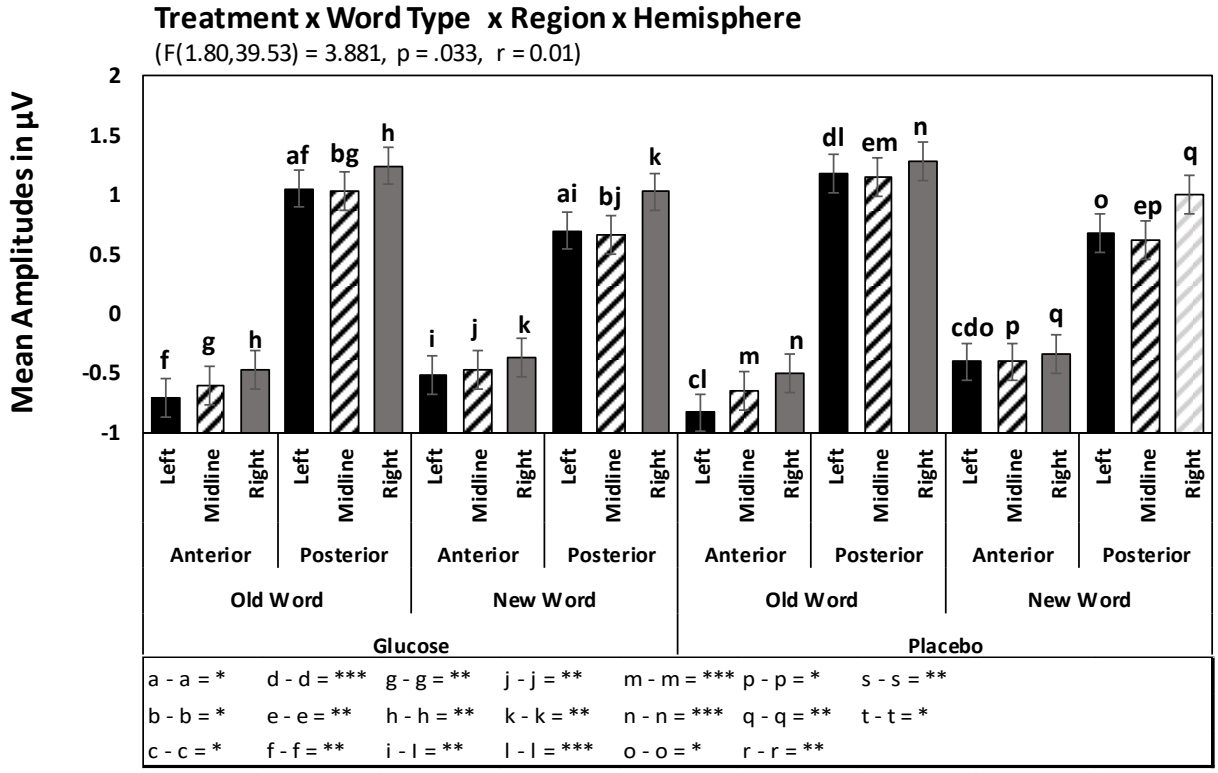
Table 5.81 Word Recognition Old/New Correct Recognitions LPC Component.
Amplitude means and SEMs depicting the treatment x word type x region x hemisphere interaction.

Treatment	Word Type	Region	Hemisphere	Mean	±	SEM
Glucose	Old Word	Anterior	Left	-0.707	±	0.247
			Midline	-0.604	±	0.230
			Right	-0.473	±	0.248
		Posterior	Left	1.052	±	0.212
			Midline	1.036	±	0.202
			Right	1.244	±	0.255
	New Word	Anterior	Left	-0.523	±	0.181
			Midline	-0.47	±	0.176
			Right	-0.368	±	0.182
		Posterior	Left	0.698	±	0.139
			Midline	0.658	±	0.170
			Right	1.024	±	0.221
Placebo	Old Word	Anterior	Left	-0.836	±	0.200
			Midline	-0.655	±	0.167
			Right	-0.502	±	0.192
		Posterior	Left	1.181	±	0.205
			Midline	1.151	±	0.211
			Right	1.284	±	0.232
	New Word	Anterior	Left	-0.408	±	0.189
			Midline	-0.408	±	0.196
			Right	-0.341	±	0.178
		Posterior	Left	0.678	±	0.169
			Midline	0.613	±	0.152
			Right	1.006	±	0.228

Table 5.82 Word Recognition Old/New Correct Recognitions LPC Component. Significant pairwise comparisons from the Treatment x Word Type x Region x Hemisphere interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition / Group	Pairwise Differences	Mean(SEM)	t(22)=	p Value
Glucose,Posterior, Left Hemisphere	Old Words more positive than New Words	Old Words (Mean 1.052, SEM 0.212)	2.441	0.024
		New Words (Mean 0.698, SEM 0.139)		
Glucose,Posterior, Midline Hemisphere	Old Words more positive than New Words	Old Words (Mean 1.036, SEM 0.202)	2.291	0.032
		New Words (Mean 0.658, SEM 0.170)		
Placebo, Anterior, Left Hemisphere	Old Words more positive than New Words	Old Words (Mean -0.836, SEM 0.200)	2.709	0.013
		New Words (Mean -0.408, SEM 0.189)		
Placebo, Posterior, Left Hemisphere	Old Words more positive than New Words	Old Words (Mean 1.181, SEM 0.205)	4.263	<0.001
		New Words (Mean 0.678, SEM 0.169)		
Placebo, Posterior, Midline Hemisphere	Old Words more positive than New Words	Old Words (Mean 1.151, SEM 0.211)	3.816	0.001
		New Words (Mean 0.613, SEM 0.152)		
Glucose, Old Words, Left Hemisphere	Posterior greater than Anterior	Anterior (Mean -0.707, SEM 0.247)	3.989	0.001
		Posterior (Mean 1.052, SEM 0.212)		
Glucose, Old Words, Midline Hemisphere	Posterior greater than Anterior	Anterior (Mean -0.604, SEM 0.230)	3.933	0.001
		Posterior (Mean 1.036, SEM 0.202)		
Glucose, Old Words, Right Hemisphere	Posterior greater than Anterior	Anterior (Mean -0.473, SEM 0.248)	3.562	0.002
		Posterior (Mean 1.244, SEM 0.255)		
Glucose, New Words, Left Hemisphere	Posterior greater than Anterior	Anterior (Mean -0.523, SEM 0.181)	4.040	0.001
		Posterior (Mean 0.698, SEM 0.139)		
Glucose, New Words, Midline Hemisphere	Posterior greater than Anterior	Anterior (Mean -0.470, SEM 0.176)	3.503	0.002
		Posterior (Mean 0.658, SEM 0.170)		
Glucose, New Words, Right Hemisphere	Posterior greater than Anterior	Anterior (Mean -0.368, SEM 0.182)	3.654	0.001
		Posterior (Mean 1.024, SEM 0.221)		
Placebo, Old Words, Left Hemisphere	Posterior greater than Anterior	Anterior (Mean -0.836, SEM 0.200)	5.253	<0.001
		Posterior (Mean 1.181, SEM 0.205)		
Placebo, Old Words, Midline Hemisphere	Posterior greater than Anterior	Anterior (Mean -0.655, SEM 0.167)	5.205	<0.001
		Posterior (Mean 1.151, SEM 0.211)		
Placebo, Old Words, Right Hemisphere	Posterior greater than Anterior	Anterior (Mean -0.502, SEM 0.192)	4.314	<0.001
		Posterior (Mean 1.284, SEM 0.232)		
Placebo, New Words, Left Hemisphere	Posterior greater than Anterior	Anterior (Mean -0.408, SEM 0.189)	3.148	0.005
		Posterior (Mean 0.678, SEM 0.169)		
Placebo, New Words, Midline Hemisphere	Posterior greater than Anterior	Anterior (Mean -0.408, SEM 0.196)	3.103	0.005
		Posterior (Mean 0.613, SEM 0.152)		
Placebo, New Words, Right Hemisphere	Posterior greater than Anterior	Anterior (Mean -0.341, SEM 0.178)	3.445	0.002
		Posterior (Mean 1.006, SEM 0.228)		
Glucose, New Words, Posterior	Right Hemisphere more positive than Midline	Right (Mean 1.1024, SEM 0.221)	4.207	0.001
		Midline (Mean 0.658, SEM 0.170)		
Placebo, Old Words, Anterior	Right Hemisphere more positive than Left	Left (Mean -0.836, SEM 0.200)	3.929	0.002
		Right (Mean -0.502, SEM 0.192)		
Placebo, New Words, Posterior	Right Hemisphere more positive than Midline	Right (Mean 1.006, SEM 0.228)	3.169	0.013
		Midline (Mean 0.613, SEM 0.152)		

Figure 5.41 Word Recognition Old/New Correct Recognitions LPC Component. Significant pairwise comparisons from the Treatment x Word Type x Region x Hemisphere interaction. Figure key shows pairwise comparisons and significance levels.. Bars show standard error.



From the demand x region interaction (F(1,22) = 4.59, p = .043, r =0.04), see Table 5.78 above and Table 5.83 below for interaction means and SEM. Pairwise comparisons for interaction effects of demand and region can be seen in Table 5.84 below and Figure 5.42 below. Effects of demand effects elicited enhanced posterior LPC amplitudes following low demand encoding compared to high demand encoding.

Regional effects on the interaction revealed posterior LPC amplitudes were greater than the anterior region following both low and high demand encoding.

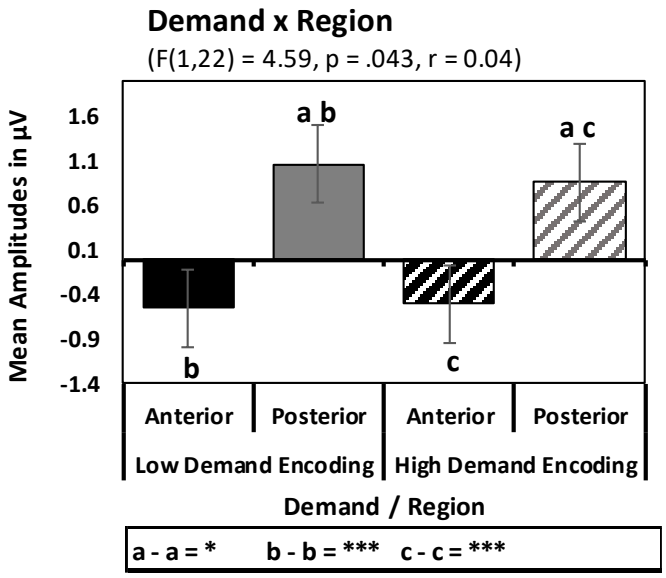
Table 5.83 Word Recognition Old/New Correct Recognitions LPC Component. Amplitude means and SEMs depicting the demand x region interaction.

Demand	Region	Mean	±	SEM
Low Demand Encoding	Anterior	-0.55	±	0.180
	Posterior	1.068	±	0.166
High Demand Encoding	Anterior	-0.499	±	0.166
	Posterior	0.869	±	0.174

Table 5.84 Word Recognition Old/New Correct Recognitions LPC Component. Significant pairwise comparisons from the Demand x Region interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown.

Condition	Pairwise Differences	Mean(SEM)	t(22)=	p Value
Posterior Region	Low Demand > High Demand	Low Demand (Mean 1.068, SEM 0.166)	3.015	0.006
		High Demand (Mean 0.869 SEM 0.174)		
Low Demand Encoding	Posterior greater than Anterior	Anterior (Mean -0.550, SEM 0.180)	4.801	<0.001
		Posterior (Mean 1.068, SEM 0.166)		
High Demand Encoding	Posterior greater than Anterior	Anterior (Mean -0.499, SEM 0.166)	4.096	<0.001
		Posterior (Mean 0.869, SEM 0.174)		

Figure 5.42 Word Recognition Old/New Correct Recognitions LPC Component. Significant pairwise comparisons from the Demand x Region. Figure key shows pairwise comparisons and significance levels. Bars show standard error.



There was a word type x demand interaction (F(1,22) = 5.246, p = .032, r =0.02), see Table 5.78 above and Table 5.85 below for interaction means and SEM. Pairwise comparisons for interaction effects of word type and demand can be seen in Figure 5.43 below.

Word type effects revealed that following low demand encoding old words elicited higher LPC amplitudes relative to new words.

Demand effects of the interaction showed that old words had higher LPC amplitudes following low demand compared to high demand. Interestingly, there was no effect of demand on new words.

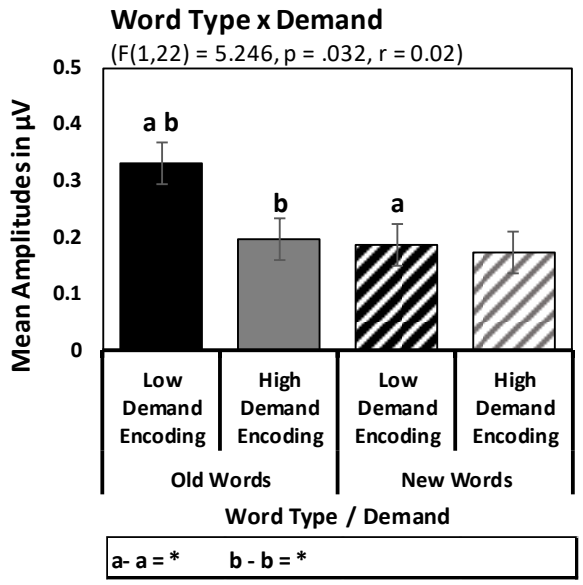
Table 5.85 Word Recognition Old/New Correct Recognitions LPC Component. Amplitude means and SEMs depicting the word type x demand interaction.

Word Type	Demand	Mean	±	SEM
Old Words	Low Demand Encoding	0.331	±	0.047
	High Demand Encoding	0.198	±	0.041
New Words	Low Demand Encoding	0.187	±	0.047
	High Demand Encoding	0.172	±	0.040

Table 5.86 Word Recognition Old/New Correct Recognitions LPC Component. Significant pairwise comparisons from the Word Type x Demand interaction. Pairwise differences, means and SEMs, t-values, degrees of freedom and p-values are shown .

Condition	Pairwise Differences	Mean(SEM)	t(22)=	p Value
Low Demand Encoding	Old Words > New Words	Old Words (Mean 0.331, SEM 0.047)	2.979	0.007
		New Words (Mean 0.198, SEM 0.041)		
Old Words	Low Demand > High Demand	Low Demand (Mean 0.331, SEM 0.047)	3.167	0.005
		High Demand (Mean 0.198, SEM 0.041)		

Figure 5.43 Word Recognition Old/New Correct Recognitions LPC Component. Significant pairwise comparisons from the Word Type x Region. Figure key shows pairwise comparisons and significance levels. Bars show standard error.



5.6.2.2.1 Summary of Word Recognition Old/New ERP Data Results

FN400 component (310-480ms latency range) analysis showed a significant interaction between glucoregulation, treatment, word type, valence and hemisphere revealing that following glucose poorer regulators had higher FN400 amplitudes than did better regulators for old and new negative words and new positive words at midline and left hemisphere electrodes. Following placebo, poorer regulators had higher FN400 amplitudes than better regulators for new neutral words only. Poorer regulators had higher right hemisphere old negative words and left hemisphere new positive words following glucose. This was reversed for better regulators who had higher FN400 amplitudes following placebo. Following glucose, poorer regulators had higher right hemisphere FN400 amplitudes for old negative words compared to new negative words. Overall FN400 amplitudes were greater at right hemisphere electrodes. There was also an interaction between word type, region and hemisphere which indicated unexpectedly that the anterior FN400 was greater for old words compared to new words. Tentatively, an explanation for this may be that the greater FN400 anterior amplitudes are indicative of episodic recollection or memory strength. Conversely, the posterior FN400 was greater for new words relative to old words; one explanation for this may be that as the increased posterior neural activity generally associated with recollection is seen in the later time window, it was not evident in the earlier latency window of the FN400. The main effect of glucoregulation showed poorer regulators elicited higher FN400 amplitudes than did better

regulators. The main effect of glucoregulation showed that better regulators elicited lower FN400 amplitudes than poorer regulators.

LPC component (470-780ms latency range) analysis showed a significant interaction between glucoregulation, treatment, word type, valence, and hemisphere. This indicated that following glucose, poorer regulators had greater old neutral word, right hemisphere LPC amplitudes than did better regulators. Similarly poorer regulators elicited greater new negative words at midline and new neutral words at both midline and right hemisphere electrodes than did better regulators. For better regulators, placebo resulted in higher right hemisphere amplitudes than glucose in response to new neutral words; this was reversed for poorer regulators who elicited greater LPC amplitudes following glucose. Following glucose, better regulators elicited higher midline amplitudes for new neutral words in comparison to old neutral words. Differentially, following placebo poorer regulators had higher left hemisphere LPC amplitudes for old positive compared to new positive words. There was also an interaction between treatment, word type, region and hemisphere which showed that following glucose, old words evoked higher left and midline posterior LPC amplitudes compared to new words. In the anterior region, new words had higher left hemisphere amplitudes than old words following placebo. Posterior left and midline LPC amplitudes were greater for old words compared to new words and in regional terms posterior amplitudes were greater than anterior amplitudes across all conditions. In addition, the interaction between demand and region showed that following low demand encoding posterior LPC amplitudes were greater than following high demand encoding. Posterior LPC amplitudes were greater than anterior amplitudes following both low and high encoding conditions. Finally, there was an interaction between word type and demand revealing that following low demand encoding old words elicited greater LPC amplitudes than did new words. Old words, but not new words elicited higher LPC amplitudes following low demand relative to high demand encoding.

5.6.3 Word Recognition Remember/Know Analysis

Insufficient trials for subjective ‘Remember’ or ‘Know’ responses of correct recognitions across the valence and demand variables meant that averages could not be produced for analysis.

5.7 Discussion

5.7.1 Summary of Main Findings

The principal aim of this chapter was to explore the potential of utilising measures of glucoregulatory control in young non-diabetic adults as an early risk marker of T2DM. To achieve this participants' risk of developing T2DM was assessed by incorporating items known to be T2DM risk factors into the health screening questionnaire. Evaluation of glucoregulatory control was facilitated by a median split based on participants evoked blood glucose levels. To investigate the potential effect of glucoregulatory control and circulatory blood glucose levels, episodic memory and additionally, attentional resources as assessed via the SART conflict task were conducted. Both behavioural and neurophysiological measures, specifically ERP correlates of episodic memory, were utilised to investigate the impact of glucoregulation and ingested glucose on the accuracy of episodic memory and inhibition. Additionally, to investigate whether glucoregulation or glucose ingestion mediated memory type, participants' subjective assessment of the memory strength of correct recognitions of old words was assessed via the recollection and familiarity paradigm; unfortunately subjective ERP data was not available, see section 5.6.2.2.1 for an explanation of this. In light of no differences being found in heart rate between better and poorer regulators in chapter 4, this chapter further explored the relationship between glucoregulatory control and cardiovascular measures by assessing measures of heart rate variability. Low HRV is associated with poor health, the development of metabolic syndrome, coronary heart disease (Aso et al., 2006) and cardiovascular autonomic neuropathy has commonly been shown to be comorbid in individuals with T2DM. HRV was monitored pre-tasks in the placebo visit when participants were in a fasted state. This chapter also explored whether there was mediation of heart rate measures (in BPM) and HRV of glucoregulation and glucose ingestion in response to the encoding of emotional words.

5.7.1.1 Blood Glucose

Based on their iAUC for blood glucose response over the OGTT, calculated from the OGTT on the practice visit, a median split was used to divide participants into better glucoregulators and poorer glucoregulators. A one-way ANOVA, conducted on better vs. poorer glucoregulators, confirmed that response to the glucose load was highly significantly different between the two groups and as such demonstrated that the median split was a valid division of the glucoregulator type variable. Analysis of test day data found a significant difference, with better glucoregulators having lower levels of

blood glucose overall. Also on test days, analysis of test visit baseline blood glucose levels found that there was a significant difference in baseline measures for the placebo visit, with poorer regulators having slightly high levels of blood glucose. This finding differed from chapter 4 where test day blood glucose levels did not differ significantly between better and poorer regulators. An appealing explanation for this may be that as the mean iAUC of participants' blood glucose levels was slightly higher for chapter 5, this may have represented a subtle difference in measures of glucoregulation. This would potentially provide evidence for the argument that glucoregulatory control was indeed having an impact at this pre-clinical level. A highly significant treatment x time interaction confirmed that circulatory blood glucose levels were effectively elevated by the glucose dose during the testing period.

5.7.1.2 T2DM Risk Score and Glucoregulation

The outcome of this analysis provided evidence for the research question, that there would be a positive relationship between glucoregulatory control, as indicated by iAUC measures, and T2DM risk scores. These findings provided evidence for the efficiency of using a questionnaire based on known T2DM risk factors alongside glucoregulatory control measures as a means of identifying the potential risk of developing T2DM. The outcomes revealed that known associable T2DM risk factors had a significant positive relationship with blood glucose measures (iAUC) taken via an oral glucose tolerance test, with risk scores rising as iAUC rose. As these effects have been observed in this population of healthy young adults, this positive relationship between these measures provides evidence for the efficacy of the risk score assessment model in terms of preventative interventions which may be put into place prior to the onset of T2DM. An additional application of this risk assessment tool would be in identifying and recruiting individual for further research.

5.7.1.3 Heart Rate and Heart Rate Variability

Following on from the non-significant but potentially interesting findings of Chapter 4 (see section 4.5.1.2.1 for result), Chapter 5 further explored whether poorer regulators would have higher heart beats per minute than better regulators. Whilst no support for effects of glucoregulation were seen in the present chapter, as found in the previous chapter, poorer regulators mean heart rate was elevated compared to better regulators. A treatment effect provided evidence that mean heart rate, was elevated following glucose for the 60 second baseline assessment prior to task commencement;

during this time, participants were asked to relax quietly, and no stimuli were presented on their computer screen.

In terms of heart rate variability, it was proposed that poorer glucoregulators would have lower heart rate variability than better regulators. Whilst no differences were seen between better and poorer regulators for either time-domain or frequency domain metrics of HRV. Correlational analysis was conducted separately for better and poorer glucoregulators. Correlational analysis between various HRV measures and iAUC found multiple negative correlations which demonstrated that as glucoregulatory control was diminishing (as seen by rising iAUC), heart rate variability was also lessening. For better regulators, these significant negative correlations with HRV were only seen relative to iAUC; however for poorer regulators, negative correlations with HRV were seen for iAUC, fasting blood glucose levels, T2DM risk scores, and baseline heart beats (BPM), please see Table 5.30for details. However, the most pertinent observation from these analyses is that when assessed in the placebo condition, these negative correlations were seen to a greater extent across the HRV variables in poorer regulators than in better regulators (see Table 5.30). Additionally, glucose was seen to be modulating outcomes to a greater extent in poorer regulators than better regulators. These findings provide early tentative evidence that HRV is an early indicator of the cardiovascular issues present in individuals with risk of developing T2DM. There was also evidence which showed that heart rate variability metrics differed between glucose and placebo, with more significant negative relationships found following glucose, relative to placebo.

5.7.1.4 Sustained Attention to Task (SART)

There were no effects of treatment seen for the SART conflict task but evidence for the research question which asked whether better regulators would have greater overall accuracy than poorer regulators was supported by the main effect of glucoregulation. Similarly better glucoregulators, as predicted, made faster responses than poorer regulators providing more evidence for the SART task being modulated by glucoregulation. However the interaction between glucoregulation and SART type seen in the accuracy data may be ambiguous, as such, poorer regulators having more accurate NoGo responses, compared to better regulators, may just be because their slower responses were breaching the 250 millisecond NoGo time-outs (see Table 5.35 for means).This finding reflects the slower response speeds made by better and poorer regulators, to congruent relative to incongruent, Flanker trials in chapter 4.

5.7.1.5 Word Recognition Old/New

Encoding Phase Neurophysiological data outcomes (see section 5.6.1)

Treatment differences seen in N1, P3 and LPC component amplitudes demonstrated support for the research question that glucose would modulate neurological responses to memory processes. Glucose was also seen to modulate P3 component amplitudes across the 210 – 330 ms time window for poorer regulators only, which offers tentative support for glucose enhancement targeting compromised populations.

Glucoregulation differences and demand effects were seen following placebo in LPC amplitudes across the 540 – 780ms time window with glucoregulation modulating amplitudes differentially for better and poorer regulators following high demand encoding.

Behavioural data outcomes word recognition (see section 5.5.2.2.1)

Differentially from Chapter 4, there was a main effect of glucoregulation for the Old/New accuracy behavioural data which provided evidence for glucoregulatory control impacting on episodic memory accuracy, with poorer regulators making a lower percentage of accurate recognitions compared to better regulators. Tentatively, the inclusion of smokers in chapter 5 may have impacted on this significant behavioural finding, the mean iAUC of participants overall for chapter 5 was slightly elevated for this chapter compared to chapter 4. There was no evidence from behavioural accuracy for the research question which explored whether there would be an interaction between glucoregulatory control and a glucose dose, as such, there was no evidence to support glucose having a more facilitative effect on poor glucoregulators. Additionally, there was no support from the behavioural accuracy data for glucose enhancement of episodic memory.

In terms of the response reaction speed data, this supported the glucoregulation model used here, for the placebo condition better regulators has faster recognition response reaction speeds than poorer regulators, again providing evidence for differences between better and poorer regulators.

Neurophysiological data outcomes word recognition (see section 5.6.1.4.1)

Whilst no support for an interaction between glucoregulatory control and a glucose dose was seen in the behavioural data, there was evidence to support this in the word recognition ERP data for the

FN400 and the LPC components. Differences were seen in ERP amplitudes between better and poorer glucoregulators, with poorer regulators having an enhanced FN400 across the 310 – 480ms time window and LPC across the 470 – 780ms time window for multiple conditions following glucose, relative to better regulators. This may offer support for the proposition that compromised populations are targeted by glucose facilitation . These neurological differences provide evidence for the view of Messier et al. (2011), who found that younger individuals were exhibiting cognitive impairment prior to reaching the pre-diabetic stage (see Table 1.1 for details) of glucoregulatory control.

5.7.2 Limitations

It was not possible to replicate the neurophysiological findings of the subjective Remember/Know data from chapter 4 because of the introduction of the secondary task. The addition of this further variable meant that there were insufficient trials to create averages. However, as this was a purely technical consequence of the EEG software, the behavioural data was unaffected. For the future this could be resolved by increasing the numbers of the stimuli in each of the four word lists in the word recognition blocks (see Figure 5.1 for a schema of tasks for clarification). In the SART response inhibition task a confounding issue may have been length of the time-outs between trials. Poorer regulators were seen to make more accurate NoGo SART responses than better regulators. This may be because the faster responses by better glucoregulators allowed them to register more incorrect NoGo responses, whereas for poorer regulators their slower responses breached the 250 millisecond time-out and as such registered more correct NoGo responses. Resolving this would need careful consideration of the time-out period for any future research. Differentially to chapters 2 and 3, which used between-groups designs, no baseline measures of cognitive tasks were taken for chapter 5 which utilised a within-groups design based on treatments, glucose or placebo drinks were administered prior to testing. Comparisons were made across treatment conditions rather than participants performing a baseline assessment at each visit. The rationale for this was that as the sessions already lasted for a minimum of 1.5 hours, considering the lengthy capping process, blood sampling and drink consumption and absorption, adding a further 45 minutes of sitting still to avoid disturbance of EEG and ECG electrodes would have been tiring and uncomfortable for participants. Additionally, and importantly the electrical impedances of the EEG electrodes, which were all kept to a minimum, tend to drift with time and movement, and it was felt that as this would all be reflected

in the post-treatment data, comparison between baseline and post-treatment would not have been robust.

5.7.3 Conclusion

The main objective of chapter 5 was to explore whether pre-clinical levels of impaired glucoregulatory control may be identified as a potential early marker of T2DM. This would offer the opportunity to identify individuals who are at risk of developing T2DM, and who may be in the early stages of the cognitive decline which is often comorbid with glucoregulatory disorders.

Strong evidence of a positive relationship between glucoregulation and T2DM risk was seen in the current chapter with T2DM risk scores rising with participants' iAUC measure of glucoregulatory control, as such, individuals with poorer glucoregulatory control were potentially at higher risk of developing T2DM. This finding provides support for the 'risk score' assessment model used here which may be used as a cost-effective, preventative intervention to identify potential risk at the pre-clinical stage and before the onset of T2DM.

The physiological effects of glucoregulatory control were further explored in this chapter and as in chapter 4, no differences in HR beats per minute were seen between better and poorer glucoregulators. However, ingested glucose was seen to elevate heart rate for both groups and again, as in chapter 4, although the difference was not significant, poorer regulators had higher heart rate relative to better regulators following glucose. In terms of heart rate variability, this chapter provided support for a relationship between heart rate variability and glucoregulatory control, which demonstrated that as glucoregulatory control was diminishing, heart rate variability was also lessening. Jaiswal et al (2013) who observed early indications of CAN with low HRV in the diabetic subjects which the authors argued was driven by elevated blood glucose levels; chapter 5 extends this research to a population of non-diabetic, healthy but potentially at risk of T2DM young adults (aged 18 – 35). These findings also supports and adds to the research by Penčić-Popović et al., (2014) who found that that healthy non-diabetic individuals (mean age 50 ± 14.4 years) who were observed to have increased risk of T2DM were also seen to have impaired heart rate variability, specifically those with higher risk scores were seen to have lower values for parasympathetic modulation (RMSSD, pNN50 and High Frequency (HF)) and sympathetic modulation (Low Frequency (LF)) with these relationships being found in a population of young adults. The current chapter extends these findings to a population of young, healthy but at risk of T2DM individuals and furthermore that

glucose ingestion diminishes measures of heart rate variability differentially between better and poorer glucoregulators, and to a greater extent in poorer glucoregulators (see Table 5.30). This finding also provides evidence that HRV metrics may be potentially used as a cost-effective early assessment for the potential of individuals with T2DM to develop cardiovascular disorders.

Inhibition differences between glucoregulation groups was also evidenced in this chapter, with better regulators making faster responses to the SART conflict task. These differences support the view that decrements in inhibition are commonly seen in those populations who exhibit poor glucoregulation, such as the lack of self-control or impulsivity seen in individuals with schizophrenia (Leung et al., 2014). These differences in inhibition between glucoregulation groups are commensurate with the view that executive function such as inhibition is challenged by poor glucoregulation (Benton & Donohoe, 2004).

This chapter also set out to ascertain whether glucoregulation had an impact on episodic memory processes. Whereas chapter 4 found no evidence of glucoregulation differences in the behavioural data, the current chapter found better regulators to be more accurate and have faster response RTs relative to poorer regulators. Further exploring the concept of glucoregulation differences, by specifically exploring whether there was an interaction between glucoregulatory control and glucose ingestion, neurophysiological data from chapter 5 provided evidence for the notion that ingested glucose targets compromised populations. Following glucose, poorer regulators were seen to elicit greater FN400 and LPC amplitudes, during the recognition phase, relative to better regulators.

Chapter 5 addressed the question of whether glucose facilitation was demand or domain related with the inclusion of a high-effort secondary task during the encoding phase. Support for the demand hypothesis was seen in the neurophysiological data with glucoregulation modulating LPC amplitudes differentially for better and poorer glucoregulators following high demand encoding and placebo. Whilst no glucose dose was involved in this difference, it could tentatively be extrapolated that the increased cognitive demand was mediating levels of cerebral glucose available to participants. In terms of treatment effects, in Chapter 5 glucose was found to be modulating P3 amplitudes for poorer regulators only, this may provide evidence for glucose facilitation during the encoding phase when the extra demand of the mouse tracking task was in play. Additionally, this finding provides evidence for the conjecture that glucose facilitation preferentially targets individuals with challenged glucoregulatory control.

The final objective of the current chapter was to identify whether ERP components would differ in amplitude between better and poorer regulators. Support was seen for this in both the encoding and recognition phases of the episodic memory process. This finding provides strong neurological evidence that these early, glucoregulation differences are potentially mediating encoding and recognition phases of memory. This may, potentially be an early marker of the cognitive decrements associated with poor glucoregulatory control.

The outcomes of this chapter showed that individuals in the poorer regulation group had diminished performance for episodic memory and had slower responses for the SART inhibition task. Additionally poorer regulators had diminished heart rate variability compared to better regulators. Chapter 5 offers overarching evidence of cognitive, physiological, and neurological effects of glucoregulation being observable in young, healthy non-diabetic adults with pre-clinical decrements in glucoregulatory control. Perhaps the most striking finding of chapter 5 was evidence of the relationship between T2DM risk scores and glucoregulatory control, which significantly aligned poor glucoregulation with diminished heart rate variability.

The majority of individuals who develop T2DM are not aware of their glucoregulation issue until the disease has progressed to the stage where symptoms of metabolic syndrome, a precursor of T2DM are becoming apparent. Conditions such as obesity, insulin resistance, hypertension and impaired HRV and cognitive deficits are all associated with the development of metabolic syndrome, and all these factors can be ameliorated by making healthy lifestyle choices. The findings of this chapter provide evidence that risk of the development of the above factors can be detected well in advance of cumulative physical and cognitive damage becoming pathological.

Raising awareness of these risks, would enable individuals to monitor their lifestyle choices and potentially prevent metabolic problems before they arise. Non-invasive self-checks such as T2DM risk score questionnaires, assessment of HRV (easily monitored via fitness tracking watches). Self-screening of blood glucose levels can also be done easily using urine glucose strips and whilst these are not as effective as blood-sampling (Storey et al., 2018) they are a cost effective blood glucose screening tool. These measures would enable individuals to put into place self-help interventions such as weight loss, smoking cessation, dietary changes, and improved exercise regimes. Educating young adults about the risks involved in their lifestyle choices could potentially result a reduction of T2DM across their generation in later life.

6 General Discussion

6.1 Summary of the Objectives of this Thesis

This section includes summaries of the aims and objectives of each of the four experimental chapters. A brief outline of the outcomes, and how these contributed to building rationales which would take the aims and objectives forward into the following chapter.

The main question which the thesis aimed to address was whether the early cognitive decrements associated with poor glucoregulatory control are visible in healthy young non-diabetic adults. Episodic memory and attentional resources have been referenced in the literature as being sensitive to glucose and glucoregulatory control. There is also a wealth of evidence that the memory decrements found in individuals with glucoregulatory disorders are in part, a result of insulin intolerance which is known to impact on hippocampal mediated memory processes. This thesis explored cognitive, glucoregulatory, neurophysiological and cardiovascular factors, with the objective of establishing a T2DM risk profile which could be applied to facilitating the prevention of individuals progressing to the disease. Participants' performance on episodic memory and attentional conflict tasks was assessed and their neurological, cardiovascular and glucoregulatory metrics were monitored whilst glucose and placebo treatments were manipulated. These objectives were pursued by positing the following questions:

- Will manipulating the experimental and placebo treatments during episodic memory tasks provide evidence for glucose facilitation, and additionally, whether glucose enhancement is facilitated by task domain or task demand was posed.

- Is there evidence from behavioural word recognition data and neurophysiological data, of ingested glucose modulating episodic memory? and in turn, are there ERP amplitude differences between glucoregulation groups.

- To investigate whether cardiovascular decrements found in T2DM individuals are detectable in young non-diabetic adults. Cardiovascular response, as such heart rate (BPM), to neutral and emotionally valenced words was monitored, and heart rate variability (HRV) was

assessed during the encoding of neutral stimuli to see if they were differentially mediated by glucose ingestion or glucoregulatory control?

- To assess whether an individual's calculated T2DM risk score could be associated with other measures such as glucose tolerance (iAUC), heart rate variability (HRV) and resting heart rate (BPM) and fasting blood glucose levels, all of which are known to be implicated in T2DM. These assessments seek to provide evidence that potential relationships between these factors can be an early indicator of an individual's potential to develop T2DM.

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

- Chapter 2: 'An Assessment of the Efficacy of Non-Nutritive Sweeteners and Flavour Masks Used in Experimental and Placebo Drinks.'

- Chapter 3: 'Investigation of Combined Treatment Components: Does glucose Administration Mediate Episodic Memory and Inhibition Processes?'

- Chapter 4: 'The Influence of Ingested Glucose and Glucoregulatory Control on the Neurophysiological and Physiological Correlates of Episodic Memory and Inhibition in Young

- Chapter 5: 'Investigating the Impact of Elevated Type 2 Diabetes Risk on Episodic Memory Processes and Inhibition: Specifically Comparing Neurophysiological, Glucoregulatory and Cardiovascular Factors in Non-Diabetic, Healthy Young Adults Vs Non-Diabetic, Potentially at Risk Young Adults.'

6.1.1 An Assessment of the Efficacy of Non-Nutritive Sweeteners and Flavour Masks Used in Experimental and Placebo Drinks.

Chapter 2 aimed to investigate the anomalies in the literature concerning the effects of glucose administration on cognitive processes by investigating the potential impact on cognition of these treatment ingredients in isolation. In terms of the primary aim of chapter 2, the rationale was to establish guidelines for the components of experimental and placebo treatments for further chapters of this PhD programme. Significant effects of glucose, RSFOC, and lemon juice were seen, specifically the slowing or speeding up of response RTs differentially across cognitive tasks. Treatment effects

(but no significant post hoc findings) were found for episodic memory tasks (picture and word recognition measures). In the role of flavour masking agents, lemon juice and RSFOC are commonly employed in both the experimental and the placebo treatment, this may suggest that we are potentially seeing a modulatory effect of added treatment ingredients rather than, or in addition to, a glucose effect. Aspartame was seen to increase reported mental energy in comparison to water (see 2.3.3.1), with glucose and RSFOC both mediating the number of correct serial 7 subtractions in comparison to water. These findings further highlight the potential cognitive effects of previously presumed inert components.

Interestingly, in the same way that glucose is not seen to globally affect cognition, these treatment ingredients also appear to selectively target specific cognitions. Outcomes of chapter 2 suggest that caution should be taken when selecting ingredients of experimental and placebo treatments and that these potential choices may depend on the aspect of cognition being investigated. In particular, as effects are seen for the placebo ingredients, caution is needed when making comparisons across studies. Findings of chapter 2 suggest that these treatment ingredients are not, as previously thought, cognitively inert. However, whilst these inconsistencies in individual drink ingredients may go some way to explaining the anomalies in the extant glucose literature, further research is needed to explore the effects of combining these ingredients.

Moving forward, the primary aim of chapter 3 was to investigate episodic memory for emotional stimuli by exploring the mechanisms of the recollection and familiarity components of word recognition memory via the 'remember-know' paradigm (Tulving, 1985). Chapter 2 revealed that, in terms of episodic memory, lemon juice as a flavour mask influences cognition, whereas Robinsons Sugar Free Orange produced limited effects across any of the cognitive domains explored in this chapter.

To further explore the efficacy of drink ingredients, chapter 3 investigated these ingredients in combinations of sweeteners and flavour-masking agents commonly used in the glucose literature.

6.1.2 Investigation of Combined Treatment Ingredients: Does glucose Administration Mediate Episodic Memory and Inhibition Processes?

The objectives of chapter 3 were twofold, primarily this chapter built on the findings of chapter 2 and moved forward to identify appropriate treatment combinations which would fulfil the requirement

of using drink ingredients which were, apart from the glucose dose, cognitively inert. The research question which addressed this, posited that any cognitive effects arising from the drink combinations containing previously assumed inert ingredients, would indicate their unsuitability for use as placebo treatments. As no treatment effects, involving those ingredients which were believed to be inert, were found in chapter 3, no definitive conclusion can be drawn. In the light of the findings of chapter 2 regarding evidence of aspartame, lemon juice, and Robinsons Sugar Free Orange Cordial effects it seemed to be judicious to investigate the combination of treatment components prior to moving forwards to chapters 4 and 5 using these ingredients for experimental and placebo treatments.

The second research question addressed by chapter 3 aimed to elucidate whether glucose facilitation was subserved by task demand. The task demand hypothesis (see section 1.5.2.6.1.1 for an explanation) postulates that glucose enhancement is only seen when the tasks being performed require a high intensity of cognitive demand (Brandt, Gibson, & Rackie, 2013; Fairclough & Houston, 2004; Kennedy & Scholey, 2000; Riby, 2004; Scholey et al., 2013; Scholey, Harper, & Kennedy, 2001; Scholey, Laing, & Kennedy, 2006b; Sünram-Lea, Foster, Durlach, & Perez, 2002). Chapter 3 explored the notion that emotional stimuli evoked a memorial advantage. It was conjectured that, based on the proviso that the emotionality of the stimuli would elevate blood glucose levels (Parent, et al., 1999; Scholey, et al., 2006) that any glucose enhancement for emotionally valenced stimuli would be more global and would be observed in the subjective remember/know paradigm data for both recollection and familiarity. On the other hand, if glucose facilitation was related to task domain and facilitation was subserved by the hippocampus, (see section 1.5.2.6.1.1 for more detail of the theory) then enhancement would be seen for recollection only. Whilst the use of this paradigm has previously displayed mixed results in the glucose enhancement literature (Scholey, MacPherson, Sünram-Lea, Elliott, Stough, Kennedy, et al., 2013; Smith & Foster, 2008; S. I. Sünram-Lea, et al., 2008), no effects of glucose were seen in chapter 3, offering no definitive support for either the demand or the domain hypotheses. However, evidence from response reaction speeds to old and new words provided tentative support for the cognitive demand paradigm. Slower responses were made to negative and positive words, relative to neutral words, which may be an indication that the variation in the emotionality of the stimuli evoked a more global demand on attentional resources, which in turn, slowed response speeds. However, as there was no significant effect of glucose seen here, it may be that the variation of emotionality of the stimuli was not sufficiently demanding to invoke a demand related glucose response.

Speculatively, the complexity of the seven x treatment groups between-groups design utilised in chapter 3 may have been masking any potential effects of ingested glucose and to clarify this further, exploratory analyses was conducted on overall accuracy (see section 3.4 for details), however no glucose effects were found.. Scholey et al., (2013) reported that glucose enhanced performance in the presence of high demand, with diminished performance following glucose and low demand. This may suggest that the demand characteristics of the tasks employed in chapter 3 were not sufficient to evoke an effect of glucose, or that any effects were too subtle to be detected in the behavioural data. The between-groups design used in chapters 2 and 3 to investigate the treatment ingredients was not ideal, although necessary due to logistical constraints (a within-groups design would have required 7 x test visits). However, employing a between-groups design was somewhat mitigated by the fact that baseline measures were assessed. Chapter 4 improved on this by strengthening the design of the experiment. By using a randomised placebo controlled within-groups design, the possibility of between-group differences was removed and provided participant data in both the placebo and glucose conditions.

Similarly for the sustained attention/inhibition task, chapter 3 explored whether glucose administration would modulate the accuracy of responses. Evidence that the Flanker paradigm was effective was shown by diminished accuracy for No/Go conflict responses, and incongruent responses when compared to congruent responses. Increased response speeds were also achieved for congruent, relative to incongruent responses. However, no glucose effects were seen for this task, providing no support for glucose modulating attentional resources.

Previous research has suggested that ingested glucose preferentially targets individuals with challenged glucoregulatory control, implying that glucoregulation impacts on glucose facilitation, and that a relationship exists between glucoregulation and performance on episodic memory tasks (Messier, et al., 2011) and executive functions such as inhibition (Benton & Donohoe, 2004). Moving forward from chapter 3, introducing measures of glucoregulation provided a rationale for investigating whether non-clinical decrements in glucoregulation, which may be present in a cohort of young, healthy, non-diabetic adults are already impacting on cognition. As no glucose effects were seen in chapter 3 and based on the proposition that any facilitative effects may have been too nuanced to be detected in behavioural data, chapter 4 introduced neurophysiological measures to further investigate whether ingested glucose can impact cognition in this population.

The association between cardiovascular measures and the cognitive decrements often observed in individuals with poor glucoregulatory control(see section 1.4.1.1.1) has not received much investigation but may account for some of the findings in the literature which suggest that heart rate and recovery rate performance may be a predictor of T2DM (Jae et al., 2016), and may be linked to insulin resistance (Panzer et al., 2002) . Chapter 4 also aimed to identify glucoregulation differences in heart rate, which may be an early indicator of impaired glucose tolerance and T2DM, in young, non-diabetic adults.

6.1.3 The influence of Ingested Glucose and Glucoregulatory Control on the Neurophysiological and Physiological Correlates of Episodic Memory and inhibition in Young Non-Diabetic Adults

The principal aim of chapter 4 was to augment current knowledge of potential early onset cognitive decrements which are often seen to be comorbid with poor glucoregulatory control. In view of the lack of behavioural evidence in chapter 3 of these early deficits in the cohort of young healthy adults, chapter 4 used neurophysiological and physiological measures to explore differences in glucoregulatory control. To achieve this objective EEG, ECG and OGTT measures of glucose tolerance were employed. Chapter 4 assessed participants glucose tolerance via an OGTT, following which participants were assigned to 'better' and 'poorer' glucoregulation groups (see section 4.5.1). Further physiological assessments in chapter 4 were conducted via ECG collection of heart rate data (see section 4.5.1.2.1). One advantage of an ERP study over behavioural studies is that neurophysiological data can be recorded during the encoding phase of recognition tasks. This gave an additional opportunity to explore potential differential processing effects between glucoregulation groups.

Four ERP components (P1, N1, P3 and LPC) were analysed during the encoding phase, investigating the research question as to whether glucose was modulating ERP amplitudes. Secondly, whether ERP amplitudes were differentially modulated by better and poorer glucoregulators. There was no evidence for this from the P1 or N1 data for either treatment or glucoregulation effects. There was however, a glucoregulation difference in P3 amplitudes following placebo better regulators had a greater left anterior P3 compared to poorer regulators. Glucose ingestion was seen to modulate P3 responses to positive words relative to placebo. Whilst no studies thus far have published directly comparable research, the glucose modulation of P3 amplitudes seen here supports a previous study which found a relationship between glycaemia P3 amplitude differences, identifying changes in the

auditory cortex of T2DM individuals (de Freitas Alvarenga et al., 2005). Riby et al. (2008) also found that the P3 component was sensitive to glucose ingestion doing an oddball attention task. Pertinent to the exploratory nature of this thesis, the P3 differences found here supports the premise that glucoregulation differences can be seen in this population at this sub-clinical stage.

The second research question posited in chapter 4, concerned whether glucose was mediating recognition accuracy and preferentially targeting poorer regulators. There was support for the conjecture that poorer regulators' accuracy performance was enhanced by an acute glucose dose.

As in chapter 3, there was no evidence from the behavioural data to suggest that glucose or glucoregulation were modulating episodic memory. It was suggested that increased accuracy in 'recollection' would provide support for the notion that glucose enhancement was domain related and being subserved by the hippocampus. Conversely, a more global, demand specific facilitation would have seen both recollection and familiarity influenced.

In terms of the argument that glucose and glucoregulation effects may be too nuanced and hence not visible in the behavioural data, Chapter 4 explored the neurophysiological data to potentially recognise glucoregulation differences and/or effects of glucose on memory strength. The subjective remember/know paradigm was conducted on correctly recognised old words. Participants' remember judgements indicated more explicit recollective memory and their familiarity judgements were indicative of implicit memory without a strong episodic connection to the stimuli. For subjective recognitions, following glucose, poorer regulators were seen to have greater FN400 amplitudes for familiarity responses to negative words compared to better regulators. This provides evidence for the chapter 4 research question which investigated whether glucose would preferentially target poorer regulators. Interestingly, significantly greater recollection compared to familiarity judgement FN400 amplitudes were seen following glucose but not following placebo for better regulators only. Treatment effects of this interaction also demonstrated that for the aforementioned responses, poorer regulators were greater following glucose compared to placebo, reinforcing the notion that poorer regulators were benefitting from an acute glucose dose. On the other hand, following glucose, better regulators were seen to elicit greater FN400 amplitudes for responses to neutral, recollection judgements. Whilst this does not support the view that glucose administration preferentially targets poorer regulators, it does offer support for the view that in this instance glucose facilitation was subserved by the hippocampus, supporting the domain hypothesis.

In the later time-window of the LPC glucose was seen to elevate amplitudes for recollection judgements of positive words. The main effect of recognition type found LPC amplitudes were greater for recollection judgements relative to familiarity judgements, tentatively this may indicate that this increase in neurophysiological activity may be associated with memory strength in this ERP component.

Whilst no coherent evidence has emerged from the ERP data in terms of whether glucose facilitation is demand or domain related, there is tentative evidence to support the theory that poorer glucoregulators are preferentially targeted by glucose. Moreover, the key finding from the chapter 4 investigation of glucoregulation, is that in this cohort of non-diabetic young adults, glucoregulatory control is modulating the neurological correlates of episodic memory. This provides distinct evidence to support the narrative that early cognitive decrements can be detected in the poorer regulators in this population.

Chapter 4 also employed cardiovascular measures to detect glucoregulation or treatment differences and to explore this mean heart rate, in beats per minute, was assessed. There were no significant effects here of either glucose ingestion or glucoregulation. However, in terms of the glucose dose, although the difference was not statistically significant mean heart rate did accelerate following glucose relative to placebo. Moreover, this effect was greater for poorer regulators than for better regulators. Speculatively, as chapter 4 offers tentative support for differences between better and poorer regulators, and as heart rate variability (see section 1.4.1.1.1) is the cardiovascular metric which has been associated with T2DM, it seemed prudent to explore this relationship in chapter 5.

The final research question in chapter 4 concerned attentional resources and inhibition, which were evaluated via the Flanker conflict task. Based on previous research chapter 4 argued that effects of glucoregulation on sustained attention/inhibition would show poorer regulators with a diminished performance compared to better regulators, with glucose ingestion benefiting this challenged population. However, the low numbers of mistakes made for the task might imply that a ‘ceiling effect’ may have been occurring, resultant from the task not being challenging enough to evoke meaningful data. Based on the narrative that glucose enhancement is relative to task difficult for recognition memory processes, extrapolating this to attentional resources, chapter 5developed this further by increasing the task difficulty via the more stringent SART task.

The final experimental chapter in this thesis addressed the methodological limitations discussed above, and by introducing a more demanding secondary task during encoding, explored the argument that glucose facilitation occurs under conditions of increased cognitive demand. Finally, this chapter found evidence that pre-clinical levels of glucoregulatory control can impact on cognitive performance. As predicted, whilst these subtle differences were not visible in behavioural data, they were visible in the neurological data of this population of young healthy adults; Chapter 5 further investigated whether this finding is associated with T2DM risk factors.

6.1.4 The Impact of Elevated Type 2 Diabetes Risk on Episodic Memory processes and Inhibition: Comparing Neurophysiological, Glucoregulatory and Cardiovascular Factors in Non-diabetic, Healthy Young Adults Vs Potentially at Risk Young Adults

To further explore the potential to highlight individuals' risk of developing T2DM, Chapter 5 sought to establish whether there was a relationship between measures of glucoregulatory control and known T2DM risk factors. Evidence was seen for the research question exploring whether there would be a positive relationship between iAUC measures of glucoregulation and rising levels of T2DM risk was supported. The positive relationship between these two factors saw that as measured glucose intolerance rose, so did T2DM risk scores, providing strong evidence that known T2DM risk factors and measures of glucose tolerance can be effective in identifying at risk individuals. Assessment of T2DM risk scores is also a useful and cost-effective tool for targeted recruitment purposes.

In terms of cardiovascular metrics, chapter 4 did not observe any significant differences in heart rate beats per minute during exposure to neutral and emotional stimuli in word recognition tasks. However, mean HR had been elevated by glucose and poorer regulators had a higher mean heart rate compared to better regulators. Chapter 4 outcomes piloted the research questions for chapter 5, which posited that HR during the encoding phase would be modulated by glucoregulatory control and ingested glucose would elevate baseline heart rate during the 60 second calibration period prior to commencement of cognitive tasks. Chapter 5 findings followed the same pattern as chapter 4, and again no significant effects of glucoregulation or the acute 25g glucose dose were found.

Chapter 5 further explored cardiovascular measures with the introduction of assessment of heart rate variability (see section 1.4.1.1.1). Lower HRV has been reported in young adults who have increased risk of developing T2DM (Penčić-Popović et al., 2014). There were no significant differences between the glucoregulation groups across the seven measures of heart rate variability.

However, there was correlational evidence that fasted heart rate variability did indeed differ between glucoregulation groups. This showed that as the pNN50 time-domain metric of HRV got higher, T2DM risk scores decreased. This finding demonstrates that individuals with low heart rate variability, which is generally associated with poor health and specifically represents a lower ability for the parasympathetic nervous system to adapt to stress (see Figure 1.3). A further research question considered whether correlations between HRV metrics and iAUC, fasting blood glucose levels, T2DM risk score and baseline heart rate in BPM differed between glucoregulation groups and/or were impacted by ingested glucose. These analyses show that, as better regulators' measured glucose tolerance (iAUC) increased, VLF and LF measures of HRV became lower following glucose. Following placebo iAUC increased as LF/HF, or vagal tone, diminished. However, the scope of these associations was much broader for poorer regulators. Following glucose consumption, measured iAUC, fasting blood glucose levels , T2DM risk score and baseline heart rate in BPM were all negatively correlated with multiple metrics of HRV; following placebo there was a similar but less widespread picture for iAUC, fasting blood glucose levels and T2DM risk scores but not for heart rate BPM (see Table 5.30 for comprehensive outcomes of individual measures/ analyses). These findings provide evidence that the less efficient glucose tolerance of poorer glucoregulators was observed to have a greater impact on HRV. This is evidenced by more widespread negative correlations being observed after blood glucose levels were elevated by ingested glucose (see Table 5.30). This lower variability in heart rate is associated with cardiovascular autonomic neuropathy, a frequently undiagnosed comorbidity of T2DM (see section 1.4.1.1.1 for a more detailed description). The findings of the HRV analysis undertaken in chapter 5 also provides additional evidence of the potential to detect early markers of T2DM risk in a cohort of young, healthy, non-diabetic adults.

To move forward from the lack of findings for the Flanker conflict task in chapter 4, possibly due the task difficulty not having been sufficient to evoke glucoregulation differences and/or differences between glucose and placebo treatments, chapter 5 introduced the more stringent SART conflict task. Chapter 5 investigated whether poorer regulators would be less accurate and slower to respond that better regulators. It was suggested that if glucose preferentially targets poorer glucoregulators, their performance would be enhanced compared to following the placebo treatment. However, whilst the lack of significant treatment findings could not confirm preferential targeting of poorer regulators by a glucose dose, better regulators responded more quickly. This finding contributed to the evidence of glucoregulatory control impacting on cognition.

Differentially from chapter 4, where no behavioural effects of glucose ingestion or glucoregulatory control were seen, in chapter 5 the percentage of accurate recognitions of old and new words was higher for better regulators relative to poorer regulators. One attractive explanation for this may be that differentially from chapter 4, smokers were not excluded from chapter 5 and the increase in iAUC measures may have been sufficient to reveal significant differences between the glucoregulation groups. This finding demonstrates that challenged glucoregulatory control is already evoking cognitive decrements at a pre-clinical level. The lack of treatment effects from the behavioural subjective recognition data meant that no conclusions could be drawn in terms of whether glucose was preferentially enhancing recollection or familiarity judgements, and as such whether facilitation was demand or domain driven. It was not possible to pursue this question further in chapter 5 as the ERP data for subjective recognition judgements because of data collection issues, due to insufficient trials of subjective responses. However, uniquely for this area of research, ERP data was recorded during encoding, giving insight into the differential processes at this stage in memory, for better vs poorer glucoregulators.

Neurophysiological evidence from Chapter 5 offered support for the conjecture that glucose enhancement targets challenged populations, during the encoding phase of the episodic memory task glucose enhanced P3 amplitudes for poorer regulators only relative to placebo. This is an interesting finding as the P3 component has previously shown sensitivity for detection of comorbid change in the auditory cortex in T2DM individuals, demonstrating a link between glycaemia and P3 amplitudes (de Freitas Alvarenga et al., 2005). As the de Freitas et al., research used auditory rather than verbal stimuli, this outcome may not necessarily generalise to episodic memory studies but may suggest a basis for future research.

Exploratory analysis in chapter 3 revealed that glucose ingestion had diminished overall memory performance. This supported the view of Scholey et al., (2013), who suggested that task demand, rather than hippocampal mediation, was a more important determinant of glucose facilitation. A further objective of Chapter 5 was to begin to disentangle the findings of chapter 3 by investigating whether performance of a high-effort mouse tracking task during encoding would interact with ingested glucose and/or glucoregulatory control to modulate ERP amplitudes during recognition memory tasks. High demand during encoding was seen to modulate the encoding phase N1 component, which is associated with attention effects in response to visual stimuli, with greater amplitudes being elicited by poorer regulators. Both glucoregulation and treatment were seen to

modulate the LPC component, which is believed to be a significant index of both encoding and retrieval of recognition memory. There was an LPC interaction between glucoregulation, treatment, effort and hemisphere which revealed that following placebo, better regulators had enhanced left hemisphere LPC amplitudes relative to poorer regulators. Other glucoregulation differences which were related to demand and glucose were identified. Whilst these were not consistent in terms of hemisphere or region locations, they do provide tentative evidence for the research question which explored whether ERP component amplitudes would differ between better and poorer regulators. This evidence suggests that early decrements in glucoregulatory control may be seen to modulating the neurological correlates of episodic memory processes. Tentatively, glucoregulation differences in neural activity during encoding of verbal stimuli, may account for why the recall phase behavioural findings are mixed in the glucose enhancement literature.

The neurophysiological, physiological, and cardiovascular differences between better and poorer glucoregulators observed in chapter 5 provides evidence that, prior to a pre-diabetic diagnosis of T2DM, early detection of glucoregulation differences is potentially a realistic approach to identifying 'at risk' individuals.

6.2 Comparisons Between Chapters of the Impacts of Measures

6.2.1 The Impact of Glucose Administration and Glucoregulatory Control

It was evident from the blood sampling measures included in chapters 4 and 5, that the 25g dose of glucose administered to participants, was seen to effectively increase circulatory blood glucose levels at pre-test (10 mins after drink) and post-test. The manipulation of glucoregulatory control was validated and showed that poorer regulators evoked at 60 mins and via iAUC respectively, providing evidence that the procedure was appropriate, and the absorption period was sufficient to elevate circulating blood glucose levels throughout the duration of the testing sessions. This section will discuss the impact of ingested glucose and glucoregulatory control on measures employed in this thesis.

6.2.1.1 Effects on Physical and Mental State

In terms of mood, mental, and physical state assessment, there were minimal effects of treatment. In chapter 5 glucose facilitated higher levels of mental energy at post-test and an overall increase in mental stamina at the glucose test-visit, relative to the placebo visit. As these effects were not

observed in early chapters this may not be a consistent finding, although for chapters 2 and 3 this may have been a result of individual differences as between-groups designs were employed, and also lack of fasting may have had an impact. Importantly here, there were no differences between treatment groups for 'thirst' which is tentative evidence for differential levels of baseline hydration in participants not being an issue. Hydration could still have played a part due to the osmolaric properties of the treatment drinks.

6.2.1.2 Effects on Episodic Memory (including the effects of demand and valence)

In chapter 2 an overall treatment effect (but no specific treatment ingredients) was seen to target episodic memory. In chapter 3 the glucose dose again had no impact on the behavioural outcomes for episodic memory or attentional resources. Again, there were no behavioural effects of glucose for any of the episode memory or conflict tasks in chapters 4 and 5.

In chapter 5 there was an interaction effect between glucoregulation, demand and valence which identified that faster responses were made by better regulators to new neutral words, poorer regulators made faster responses to new positive and old neutral stimuli. Also, in terms of demand, accuracy was greater for old words following low demand encoding than following high demand, similarly new word accuracy was greater following low demand. As expected, due to the increased cognitive demand and dividing of cognitive resources, accuracy was diminished following high demand encoding. As there were no glucose or glucoregulation effects here this finding is evidence that the dual task paradigm was effective. In view of the minimal glucose effects found in the behavioural data for the first two experimental chapters, the rationale for introducing neurophysiological (EEG) methodology was to explore the concept that in this population effects may be nuanced and not detectable in behavioural data. This indeed was the case and direct effects of glucose were seen.

In contrast to behavioural investigations, glucose effects were observed in the ERP data collected from chapters 4 and 5. In the early latency window of the encoding phase P1 component, no effects of glucose were seen, and this was consistent across both experiments. However, glucoregulation differences were evident with differential hemispheric P1 activation in the posterior region between better and poor regulators. Whilst thus far, no directly comparable studies have reported glucoregulation effects on the P1 component, this novel finding demonstrates that P1 neural activity at the encoding stage is revealing glucoregulation differences.

Following glucose and in response to positive words, poorer regulators right hemisphere N1 amplitudes were greater, relative to following a placebo dose. This N1 glucose effect was only seen in chapter 5, Tentatively this may be an indication that the mechanism for this facilitative effect was a function of the dual task employed in this chapter, potentially offering support for the notion that glucose effects are seen when cognitive demand is high. This finding concurs with the interaction between glucoregulation, demand, valence, and hemisphere, which saw the same enhancement of the right anterior N1 during the high demand mouse tracking task. Again, this effect was observed for poorer, but not better glucoregulators.

Further glucose effects were seen for the encoding phase P3 component which supports the findings of the P3 component is associated with updating working memory during the encoding phase (Polich, 2007) REF The chapter 4 data showed that following placebo better regulators had a greater left anterior P3 than did poorer regulators. This potentially provides evidence of challenged glucoregulatory control in poorer regulators and suggests that memory impairments in this population could be occurring at the encoding phase during the updating of working memory. Evidence of impairments in the poorer glucoregulation group in the current research suggests that cognitive processes are being impacted well before glucoregulatory decline reaches clinical levels. Treatment manipulation of right hemisphere P3 amplitudes was seen following glucose for poorer regulators only; this effect was common to both chapter 4 and 5. This may support previous research which has found the P3 component to be sensitive to glucoregulatory control (see section 1.6.1.1 for a description of this component).

The encoding LPC component also revealed differential effects of treatment, chapter 4 analysis revealed that following glucose better, but not poorer regulators had a greater posterior, relative to anterior LPC. Tentatively here, as the posterior region is associated with recollection, this may indicate that a deeper level of memory encoding was occurring in better regulators in response to glucose. Evidence from chapter 5 also showed hemispheric differences between glucoregulation groups after consuming the placebo treatment. In terms of demand, following placebo better regulators had a greater left hemisphere LPC during high demand encoding than did poorer regulators; interestingly this was reversed for the right hemisphere where poorer regulators had greater LPC amplitudes compared to better regulators. Whilst no meaningful conclusions can be drawn in terms of specific hemispheres, once again these findings are indicative of differential neural activity between glucoregulation groups.

Data collected during the recognition phase for the earlier FN400 component, documented neural activity relating to correct recognitions (correct recognitions of old, previously seen words, and correct rejections of new unseen words). The FN400 component is distinguished as a frontal effect that is seen to be more negative for new, previously unseen verbal stimuli (Curran, 2000; Danker et al., 2008; Stróżak et al., 2016; Woodruff et al., 2006a). Glucose ingestion did not have an impact on the ERP data collected for chapter 4, however in chapter 5 following glucose, poorer regulators had higher FN400 amplitudes than did better regulators. This was found for both old and new correct recognitions of positive and negative words. This is an interesting finding, which tentatively may support three of the concepts explored in this thesis. Firstly, whilst no behavioural evidence was found, at the neural level glucose was seen to facilitate episodic memory. Secondly, there is support for the concept that glucose more readily facilitates glucoregulatory challenged populations. The third possibility here, is that this enhancement may potentially be due to an increase in blood glucose levels resulting from the emotionality of the stimuli. Speculatively, as there were no treatment effects observed for the FN400 in chapter 4, and as previously suggested for the N1 encoding component in chapter 5, the enhanced FN400 chapter 5 may also be linked to the dual-tasking paradigm. This would offer support for the demand hypothesis of glucose facilitation as glucose seemingly provided a benefit to poorer regulators under this increased cognitive demand. There was no impact of low or high demand encoding on the FN400 component.

In the later latency window, there were no glucose or glucoregulation effects for the word recognition LPC component seen in chapter 4. In chapter 5, there were no effects of glucose but there were multiple examples of LPC amplitudes being manipulated by glucoregulatory control. Whilst there are too many of these incidences of differences between better and poorer regulators to describe here, they provide evidence for the notion that early glucoregulatory differences, which are not detectable in the behavioural data, can be seen at a neural level.

Analysis of participants' subjective experience of recognition was based on correct recognitions of old, previously encountered words, and in this respect memory strength was being defined. There is debate in the literature as to whether explicit recollection and implicit familiarity are two distinct processes or, a continuum of memory strength (see 1.5.2.6.1 for an overview). Recognitions were defined by participants as being distinct explicit recollections, or as implicit familiar recognitions. Unfortunately, analyses of chapter 5 ERP data were not possible due to insufficient response types for each response type. In chapter 4, whilst there were no direct glucose effects, glucose was seen to

interact with glucoregulation. In response to negative words poorer regulators were seen to have a greater FN400 than better regulators for familiarity judgements, furthermore this effect was enhanced by glucose ingestion for poorer, but not better regulators. Here again there is evidence for individuals with challenged glucoregulatory control being more susceptible to glucose facilitation. Speculatively in these individuals, negative stimuli increasing blood glucose levels, may also have been contributing to the targeting of poorer regulators. Differentially, better but not poorer regulators recollection responses to neutral words elicited a larger FN400 compared to familiarity judgements following glucose. Potentially, as the FN400 is associated with implicit familiarity, this larger FN400 may be associated with the concept that glucose is preferentially targeting hippocampus mediated recollection in these better regulators.

6.2.1.3 Effects on Cardiovascular Measures

In chapter 4, glucose administration did not significantly elevate heart rate beats per minute during the encoding phase. Although, whilst the differences between treatments was not significant, mean BPM was globally higher following glucose. Additionally, whilst glucoregulation differences were not significant, poorer regulators had consistently higher BPM compared to better regulators. These trends were supported to some extent by the significant findings of chapter 5 which showed baseline BPMs, i.e., assessed at 10 minutes post treatment, were elevated by glucose. Poorer, but not better regulators had elevated heart rate in response to neutral words during high demand encoding. This may have been because poorer regulators found the task more demanding, which feeds into the rationale for employing HRV, which is a metric of an individual's ability to cope with stress, in chapter 5. There was a glucoregulation effect for poorer regulators only, who had elevated heart rate during high demand encoding compared to low demand encoding. This finding is an indication that poorer regulators have a less controlled cardiovascular response to increased demand and supports the notion that heart rate and heart rate recovery are predictors of T2DM and cardiometabolic risk in healthy men (Jae et al., 2016). Further investigation of the impact of glucose and glucoregulatory control on cardiovascular health was introduced in Chapter 5 via the assessment of heart rate variability. Better and poorer regulators did not differ in any of the time-domain or frequency domain metrics when assessed in a fasted state, nor were there any glucoregulation or treatment differences in measures which were all taken during the low-demand encoding phases. Whilst there were no direct differences in HRV between glucoregulation groups, correlational analysis (see section 5.4.4.4) revealed some interesting findings. Significant correlations between measures of HRV and

glucoregulation (iAUC), fasting blood glucose levels, T2DM risk scores and Baseline heart rate BPM were observed for both better and poorer regulators. The glucose dose also had an impact on these outcomes, with effects more frequently seen and more widespread across HRV measures in poorer regulators than in better regulators. This pattern was even more pronounced for poorer regulators when they had consumed glucose. These novel findings are important because they provide evidence for early, measurable cardiovascular differences in individuals with sub-clinical glucoregulation. Importantly, this provides a further mechanism for the early identification of at-risk individuals prior to the cognitive damage resultant from poor glucoregulatory control.

6.2.1.4 Effects on Attentional Resources/Inhibition

The Flanker inhibition tasks utilised in Chapters 3 and 4 were originally conducted to act as filler tasks between the different phases of the word recognition tasks. However, data was collected, and subsequent analysis of these data yielded some interesting findings which merited inclusion. There are mixed findings in the literature relating to glucose enhancement of conflict tasks such as the Stroop task (Stroop, 1935) and Eriksen and Eriksen's Flanker task (1974).

Analysis of Chapter 3 Flanker task data demonstrated that post-treatment accuracy was greater for left compared to right arrow Flanker arrays. Additionally, as expected accuracy was diminished for NoGo responses compared to congruent, incongruent, and neutral trials. In both chapters 3 and 4, there were no treatment effects and in in chapter 4 no glucoregulation effects were observed. For both chapters, there were faster response speeds and greater accuracy for congruent trials and for incongruent trials response speeds were slower and accuracy was decreased.

Analysis of the chapter 5 SART data did not reveal any glucose effects, but glucoregulatory control was seen to have an impact. Poorer regulators made significantly more accurate NoGo inhibition responses than better regulators. Speculatively, this apparent increased accuracy of poorer regulators for 'NoGo' trials may be explained by faster responses in better glucoregulators eliciting more NoGo errors before the 250-millisecond time-out. Poorer regulators slower RTs meant their slower error responses breached the 250-millisecond time-out and as such registered as correct 'no press' NoGo responses. In terms of response times data, faster responses were made by better glucoregulators.

The implications of the inhibition tasks utilised in Chapters 3, 4 and 5 is that poorer regulators are challenged when rapid attentional processing is required. This supports the notion that pre-clinical levels of impaired glucoregulatory control seen in a population of healthy young non-diabetic adults can potentially attenuate attentional resources and that these deleterious effects may only be seen under conditions of increased cognitive demand. The absence of glucose enhancement effects may be an indication that in this population glucose effects may be nuanced and not detectable in behavioural data. This suggests that a future line of research may be to explore these potential glucose effects using neurophysiological measures such as event-related potentials to explore whether blood glucose depletion related to self-control (Gailliot et al., 2007) is detectable at a neural level.

6.2.1.5 The Effects on Type 2 Diabetes Risk

In Chapter 5 a glucoregulatory risk assessment questionnaire was employed to assess participants' risk of developing T2DM. The rationale for this research was, that if the methodology employed in chapter 5 was effective, participants' T2DM risk score would be positively correlated with measurable items on the risk assessment questionnaire (see section 5.4.4.4). This was indeed the case and there were significant correlations between T2DM risk and glucose tolerance (iAUC), heart rate variability, fasting blood glucose levels, baseline heart rate BPM, body mass index (BMI), waist-hip ratio (WHR), and hours spent exercising per week. This provided clear evidence of the impact of negative lifestyle choices, with BMI and WHR having the strongest association.

From the evidence from previous literature and the research presented in this thesis it is evident that participants at risk from (but not experiencing clinical levels of) poor glucoregulatory control are susceptible to early indicators of cognitive decline and physiological changes (e.g., HRV) which although not easily observable in behavioural data or day to day life, are present with more nuanced physiological and neurological measures. The findings presented throughout the experimental chapters also provide evidence that even in healthy young non-diabetic adults the warning signs can already be seen in the measures listed in the previous paragraph.. This provides valuable insight to be able to more clearly identify early makers of glucoregulatory demise and the early changes occurring in the brain underlying cognitive changes prior to the associated gross accumulation (and irreversible) damage occurring.

6.3 Potential Limitations

Whilst some limitations have been highlighted in the individual experimental chapters, this section will consider the broader implications of the methodologies employed within this thesis.

The between-groups design employed in chapters 2 and 3 may have been problematic in terms of carry-over effects (e.g., practice effects, testing fatigue) from the pre-treatment to the post-treatment arrays of cognitive tasks. The nature of recruitment for these two studies precluded using a within-groups design via a multi visit testing regime. This potential issue was accounted for in the remaining two studies, but it may also be the case that these within-groups designs also had the potential for carry-over effects. Whilst there was the potential for carry-over effects from the glucose dose, the 48-hour wash-out period and the randomisation of the treatment order should have mitigated this. Additionally, participants in chapters 2 and 3 were tested in a natural state and had not been instructed to fast which may potentially have had an impact on the outcomes of the tasks. However, analysis of the assessment of mood and physical state data, which included subjective measures of hunger and thirst, did not highlight any significant differences between the groups in these measures at baseline. It may also be argued that participants were being assessed in their 'natural state' giving a more real-world insight into the effects of the treatments.

The investigations within this thesis were to some extent of an exploratory nature. As the processing of emotional stimuli during episodic memory tasks has been shown to mediate glucoregulatory control (Parent, et al., 1999; Scholey, et al., 2006), it was considered prudent to include emotionality. There were no consistent findings which may be a result of the overlap effects in chapters 3 and 4 as the experimental word lists employed in these chapters comprised of words of mixed valences. A more pronounced effect of emotionality differences may have been seen if word lists had been restricted to neutral, positive, and negative separately.

Some limitations of the conflict tasks, which were employed to explore glucose ingestion and glucoregulatory control, have already been discussed in the individual chapters (see sections 4.8.2 and 5.7.2). However, as these attentional resources tasks were originally intended as a distracting filler period between the word encoding and recognition phases of episodic memory, an additional limitation may have been that the duration of each of the 'blocks' may not have been long enough. Potentially, increasing the number of trials to increase the length of the task, may have been

sufficient to force a greater number of errors, which may have been more pronounced if participants had been required to maintain attentional focus for a longer period.

As with many psychological studies reported in the literature, the participants tested were all university students (although not solely psychology undergraduates) and as such, there may be a selection bias and it needs to be considered that a 'ceiling effect' may have been occurring. Whilst for the purpose of assessing differences in treatments and glucoregulation, consistency of cognitive ability may have been an advantage, but may not be a true representation of the target population of young adults.

6.4 Future Research

The previous section highlighted some of the potential limitations arising from the experimental chapters, however there are some interesting future research projects which could further explore the concepts discussed within this thesis.

In terms of the notion that the emotionality of stimuli may increase circulating blood glucose levels and as such, increased cerebral glucose, greater differences in the valences of words, such as only using neutral and negative stimuli and separating these between two study visits may give more insight into the underlying mechanisms of the impact of glucoregulation and ingested glucose.

Evidence was seen from glucoregulatory, EEG and cardiovascular data, that even at a sub-clinical level of challenged glucoregulation, early cognitive and structural changes are visible in a population of young, heathy non-diabetic adults. To widen the range of knowledge of the impact of impaired glucoregulatory control, some of the methodologies employed here could be applied to a wider range of populations. Participant selection based on the three diagnostic categories of glucose tolerance (see Table 1.1 for these) would allow cognitive comparisons between normal, pre-diabetic impaired glucose tolerance, and diabetes. Participants in chapters 4 and 5 were assigned to 'better' and 'poorer' glucoregulation groups. Another interesting progression would be to investigate these effects on healthy young, middle-aged, and older adults which would give insight into potentially declining glucoregulatory control across the lifespan. Assessment of HRV across the lifespan would also increase knowledge of the relationship between glucoregulation, T2DM risk factors and

cardiovascular health. Low heart rate variability, which is associated with T2DM and poor cardiovascular health, is an indicator that individuals respond less well to stress. The HRV assessment in chapter 5 was based on data collected during the low demand encoding phase, to extend this concept by comparing HRV response during a low and high effort dual task would allow insight into whether there were differences between the glucoregulation groups.

In view of the effects of glucoregulation being seen in behavioural episodic memory data for chapter 5, but not chapters 3 and 4, both of which excluded smokers, an interesting progression for further research would be to conduct a behavioural study which could further elucidate the differences in glucoregulation effects between smokers and non-smokers. This would give insight as to how great an impact nicotine consumption has on episodic memory processes and glucoregulatory control.

Conducting latency analysis, which is an alternative method of analysing ERP data, would further highlight differences. In the current work, amplitude analysis of ERP peaks based on *a priori* literature was conducted. Extending this to also explore whether there were differences in the latencies of these peaks, for example young healthy adults may elicit an ERP component peak at a slightly earlier latency than older adults, would further elucidate differences in glucoregulation groups.

6.5 General Conclusions

The principal objective of this thesis was to investigate whether the early cognitive decrements associated with poor glucoregulatory control are detectable in healthy young non-diabetic adults. Because of their known sensitivity to glucose administration and glucoregulatory differences, episodic memory and attentional resources performance provided the cognitive bases for the investigation of cognitive, glucoregulatory, neurophysiological and cardiovascular factors. Participant's performance was assessed and their neurological, cardiovascular and glucoregulatory metrics were monitored whilst glucose and placebo treatments were manipulated.

A further objective was to establish the efficacy of a T2DM risk profile which could be applied to the prevention of individuals progressing to the disease. Early identification of these subtle negative cognitive changes may help to identify and facilitate early, cost effective interventions, such as healthy eating and increased physical activity, to halt continued cumulative damage.

It was anticipated that , glucose facilitation would not be evident in the behavioural data, however for working memory in chapter 2 there were more correct Serial 7 subtractions being made following glucose. There was, however, evidence of ingested glucose modulating episodic memory processes found in the neurophysiological data. Differentially to behavioural data, EEG can collect data during the encoding phase and differences between treatments and glucoregulatory control were indeed found throughout the encoding and recognition phases of episodic memory tasks. Interestingly, there were more significant effects of glucoregulatory control seen for episodic memory processes in chapter 5 compared to chapter 4. Speculatively, as smokers were excluded from chapter 4, the impact of smoking on insulin tolerance may have been modulating effects of glucoregulation in chapter 5.

Perhaps the most interesting findings were that interactions between glucose administration and glucoregulatory control were observed. The notion that glucose has a more facilitative effect on individuals with challenged glucoregulatory control was supported, with glucose seen to be enhancing some ERP amplitudes for poorer regulators only. This theoretical construct was also reinforced by better regulators having greater P3 amplitudes than poorer regulators following the placebo treatment, supporting the concept that neural activity is impacted by challenged glucoregulatory control at this level. Previous research found that older individuals with T2DM have a diminished P3 relative to healthy older adults (de Freitas Alvarenga et al., 2005). This finding is of importance as it extends the range of this previous research to young, healthy, non-diabetic adults.

Interestingly there were no direct glucose effects on the FN400 component in chapter 4, however in chapter 5, following glucose poorer regulators elicited higher amplitudes than better regulators in response to both old and new correct recognitions of positive and negative words. This again reinforces the concept that glucose more readily facilitates challenged populations. Tentatively, another possibility here is that this glucose facilitation may potentially be due to the emotionality of the stimuli elevating blood glucose levels.

This thesis also sought to add to the current literature relating to the potential mechanisms of glucose enhancement. The introduction of the dual-task paradigm in chapter 5 revealed some interesting, although tentative, findings which may provide some support for the postulation that glucose facilitation is driven by cognitive demand. Differentially to chapter 5, no direct effects of glucose on neural activity were seen for the recognition phase FN400 in chapter 4, tentatively it may

be that whilst there were no direct effects of demand on the interaction, the glucose facilitation of the FN400 in chapter 5 may be linked to the increased cognitive demand of the mouse tracking task which was performed during the encoding phase. Also in the encoding phase, there was evidence of poorer regulators N1 amplitudes being manipulated by demand with a greater right hemisphere N1 seen during the high demand mouse tracking task compared to low demand encoding.

Conversely, there was also evidence from the implementation of the Remember/Know paradigm, which would offer support to the notion that glucose facilitation was relative to task domain. Following glucose, better glucoregulators elicited greater FN400 amplitudes in response to recollection judgements of neutral words, supporting the view that the hippocampus is heavily involved in processing recollective memory. Speculatively here, the absence of this effect in poorer regulators may give credence to the possibility that as the hippocampus is vulnerable to insulin resistance, there may already be mild impairment resultant from poorer glucose tolerance.

Investigation of cardiovascular data also demonstrated that glucoregulation differences at this pre-clinical level of glucose tolerance were visible. Whilst only a trend, poorer regulators had globally faster heart rates in beats per minute and these differences were consistent in both chapter 4 and chapter 5. Other evidence of challenged cardiovascular health was seen with poorer glucoregulators only, having elevated heart rate during high demand encoding. There were no glucoregulation or glucose differences in any of the HRV measures, however both time-domain and frequency-domain measures of HRV were found to be correlated with glucose tolerance (iAUC), fasting blood glucose levels, T2DM risk scores and baseline heart rate BPM. Importantly these effects were more wide-ranging in poorer regulators compared to better regulators. This pattern was even more pronounced for poorer regulators following glucose administration.

The T2DM risk score calculation, which was assigned to participants to provide a metric which could potentially define their risk of developing the disease, was seen to be significantly associated with glucose tolerance (iAUC), body mass index (BMI) and waist/hip ratio (WHR). Providing evidence that as glucose intolerance, BMI and WHR rose, so too did the T2DM risk score.

The new knowledge arising from this thesis, is that the economical and non-invasive combination of a simple T2DM risk assessment alongside measures of heart rate variability could be used to identify the potential to develop T2DM in individuals currently identified as young healthy non-diabetic

adults. Identifying these individuals at a pre-clinical level would allow interventions aimed at adopting more healthy life-style choices which could prevent the development of this pervasive disease.

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Appendices

2 Appendices

Appendix 2.1 Chapter 2 study participant health screen and demographic data.

Participant	Smoker	Number Per day	Sex	Age	Ethnicity	Glasses/Lenses	Handedness	Education Years	Height (metres)	Weight (Kgs)	BMI
1	Yes		F	21	Caucasian	N	Right	16	1.59	71	28.08
2	No		F	23	Caucasian	N	Right	16	1.75	133	43.43
3	No		M	20	Caucasian	N	Left	15	1.79	102	31.83
4	No		M	19	Black	Y	Right	15	1.86	103	29.77
5	No		F	19	Caucasian	Y	Right	15	1.77	109.5	34.95
6	No		F	19	Caucasian	N	Left	15	1.74	74	24.58
7	No		F	22	Caucasian	N	Right	15	1.63	57	21.45
8	No		F	19	Caucasian	Y	Right	15	1.66	73.5	26.67
9	No		F	20	Caucasian	Y	Right	15	1.62	99	37.58
10	No		F	20	Caucasian	Y	Right	15	1.7	68	23.53
11	No		F	22	Mixed	N	Left	15	1.645	84.5	31.23
12	No		F	29	Black	Y	Right	16	1.575	92.5	37.29
13	No		F	25	Caucasian	Y	Right	18	1.685	86	30.29
14	No		F	20	Black	N	Right	15	1.7	68	23.53
15	No		F	22	Caucasian	Y	Right	15	1.72	79	26.70
16	No		F	22	Black	N	Right	16	1.71	61	20.86
17	No		M	21	Caucasian	N	Left	15	1.945	85	22.47
19	No		F	34	Black	Y	Right	15	1.675	74.77	26.65
20	No		F	35	Other	Y	Right	16	1.67	82	29.40
21	No		F	21	Caucasian	Y	Right	16	1.69	70	24.51
22	No		M	19	Caucasian	N	Right	15	1.66	51	18.51
23	No		F	45	Caucasian	N	Right	16	1.705	114	39.22
24	No		F	19	Mixed	N	Right	15	1.71	96.1	32.86
25	Yes	5	F	20	Other	N	Right	15	1.5825	51	20.36
26	Yes	15	F	20	Caucasian	Y	Right	15	1.695	114	39.68
27	No		F	29	Caucasian	N	Right	21	1.63	86	32.37
28	Yes	7.5	F	21	Black	Y	Right	17	1.67	67	24.02
29	No		F	21	Other	Y	Right	16	1.645	78	28.82
30	Yes	7.5	F	20	Caucasian	Y	Right	15	1.585	53	21.10
31	No		M	21	Black	N	Right	15	1.85	77	22.50
32	No		M	22	Black	N	Right	15	1.835	75	22.27
33	Yes	10	F	46	Caucasian	Y	Right	15	1.55	61	25.39
34	No		F	24	Caucasian	N	Right	15	1.53	55	23.50
35	Yes	5	F	21	Caucasian	N	Right	15	1.675	74.77	26.65

Continued

Participant	Smoker	Number Per day	Sex	Age	Ethnicity	Glasses/Lenses	Handedness	Education Years	Height (metres)	Weight (Kgs)	BMI
36	No		F	23	Other	N	Right	16	1.605	54	20.96
37	Yes	15	F	25	Caucasian	Y	Right	11	1.7	72	24.91
38	No		F	25	Caucasian	N	Right	15	1.675	49	17.46
39	No		F	20	Caucasian	Y	Left	15	1.67	67	24.02
41	No		F	23	Black	N	Right	15	1.66	62	22.50
42	No		F	19	Caucasian	N	Right	15	1.62	71	27.05
43	No		F	20	Caucasian	Y	Right	15	1.565	69	28.17
44	No		F	23	Caucasian	N	Right	15	1.7	57	19.72
45	No		F	21	Black	N	Right	15	1.68	62	21.97
46	Yes	3	F	19	Mixed	N	Right	15	1.665	59	21.28
47	No		F	20	Mixed	N	Right	15	1.71	79	27.02
48	No		F	20	Other	N	Right	15	1.565	78	31.85
49	No		F	19	Caucasian	N	Right	15	1.61	55	21.22
50	No		F	20	Other	N	Left	20	1.595	52.5	20.64
51	No		F	21	Caucasian	N	Right	16	1.68	106	37.56
52	No		F	42	Caucasian	Y	Right	16	1.62	61	23.24
54	No		F	20	Caucasian	N	Right	15	1.685	98.25	34.60
56	No		F	21	Other	Y	Right	15	1.62	80	30.48
57	No		F	20	Other	N	Right	15	1.57	56	22.72
58	No		F	21	Black	Y	Right	15	1.7	119	41.18
59	No		F	20	Black	Y	Right	16	1.69	80	28.01
60	No		F	22	Other	N	Right	15	1.585	61	24.28
61	No		F	26	Caucasian	N	Right	16	1.56	50	20.55
62	No		F	19	Black	N	Right	15	1.575	50	20.16
63	No		F	21	Black	Y	Right	15	1.63	94	35.38
64	Yes	12.5	F	21	Caucasian	N	Right	15	1.62	62	23.62
65	Yes	12.5	F	22	Caucasian	N	Right	15	1.54	63	26.56
66	No		F	20	Caucasian	N	Right	15	1.67	56	20.08
67	No		F	21	Black	Y	Right	15	1.69	100	35.01
68	Yes	10	F	23	Caucasian	N	Right	18	1.65	55	20.20
69	No		F	27	Caucasian	Y	Right	15	1.645	69	25.50
70	No		F	20	Caucasian	N	Right	15	1.67	62	22.23

Continued

Participant	Smoker	Number Per day	Sex	Age	Ethnicity	Glasses/Lenses	Handedness	Education Years	Height (metres)	Weight (Kgs)	BMI
71	No		F	20	Caucasian	Y	Right	15	1.755	76	24.68
72	No		F	20	Caucasian	Y	Right	15	1.745	63	20.69
73	Yes	15	M	20	Caucasian	Y	Right	15	1.85	102	29.80
74	No		F	35	Caucasian	Y	Right	14	1.64	76	28.26
75	Yes	5	F	20	Caucasian	Y	Right	15	1.69	69	24.16
76	Yes	4	F	22	Caucasian	Y	Right	18	1.675	51	18.18
77	No		F	20	Caucasian	Y	Right	15	1.71	67	22.91
78	No		F	60	Caucasian		Right	13	1.65	78	28.65
79	No		F	29	Caucasian	Y	Right	15	1.62	49	18.67
81	No		F	19	Caucasian	N	Right	15	1.725	84	28.23
82	No		F	20	Other	N	Right	15	1.74	62	20.48
83	No		M	19	Caucasian	Y	Right	15	1.85	82	23.96
84	No		F	21	Caucasian	N	Right	16	1.64	85	31.60
85	No		F	20	Caucasian	N	Right	15	1.7	65	22.49
86	Yes	8	F	43	Caucasian	N	Right	15	1.665	62	22.36
87	Yes	10	F	26	Black	N	Right	17	1.74	63.5	20.97
88	No		F	21	Caucasian	Y	Right	17	1.69	87	30.46
89	No		F	19	Caucasian	Y	Left	15	1.62	69	26.29
90	No		F	20	Caucasian	Y	Right	15	1.63	49	18.44
91	No		F	19	Caucasian	N	Right	15	1.62	92	35.06
92	Yes	10	M	20	Caucasian	N	Right	15	1.775	64	20.31
93	No		F	19	Caucasian	N	Right	15	1.635	59	22.07
94	Yes	8	F	21	Caucasian	Y	Right	15	1.605	117	45.42
95	No		F	22	Caucasian	N	Right	17	1.65	97	35.63
96	No		F	21	Caucasian	N	Right	19	1.63	110	41.40
97	No		F	19	Caucasian	Y	Right	15	1.715	84	28.56
98	No		F	19	Caucasian	N	Right	15	1.71	75	25.65
99	No		F	19	Caucasian	N	Right	15	1.785	69	21.66
100	No		F	22	Caucasian	N	Right	16	1.68	64	22.68
101	No		M		Caucasian	N	Left	15	1.705	74	25.46
102	Yes	12.5	F	20	Caucasian	N	Right	15	1.71	106	36.25
103	Yes	6	F	19	Caucasian	N	Right	15	1.74	111	36.66
104	Yes	10	F	21	Caucasian	N	Right	15	1.615	80	30.67

Continued

Participant	Smoker	Number Per day	Sex	Age	Ethnicity	Glasses/Lenses	Handedness	Education Years	Height (metres)	Weight (Kgs)	BMI
105	No		F	20	Caucasian	Y	Right	15	1.6	51	19.92
106	No		M	20	Caucasian	N	Right	16	1.83	70.5	21.05
107	No		M	21	Caucasian	N	Left	14	1.87	76	21.73
108	No		F	24	Caucasian	N	Right	15	1.57	57	23.12
109	No		F	20	Caucasian	N	Right	16	1.61	49.5	19.10
110	No		F	29	Other	Y	Right	15	1.46	49	22.99
111	No		F	19	Caucasian	Y	Left	15	1.585	66	26.27
112	No		F	20	Caucasian	N	Right	15	1.675	70.5	25.13
113	No		F	21	Caucasian	Y	Right	15	1.605	45	17.47
114	No		F	19	Other	N	Right	14	1.505	39.5	17.44
115	No		M	22	Caucasian	N	Right	15	1.835	81	24.06
116	No		F	19	Black	N	Right	15	1.545	69	28.91
117	No		F	21	Black	N	Right	15	1.615	60	23.00
118	No		F	20	Black	N	Right	15	1.58	55	22.03
119	No		F	20	Caucasian	Y	Right	15	1.45	61	29.01
120	Yes	18	F	21	Caucasian	N	Right	15	1.74	124	40.96
121	No		F	43	Caucasian	N	Right	15	1.68	108	38.27
122	No		F	19	Caucasian	Y	Left	15	1.7	52	17.99
123	Yes	8	F	22	Caucasian	Y	Right	11	1.67	87	31.20
124	No		F	31	Caucasian	Y	Right	15	1.66	75	27.22
125	Yes	5	F	25	Caucasian	N	Right	15	1.73	57	19.05
126	No		F	20	Caucasian	Y	Right	15	1.67	82	29.40
127	No		F	20	Black	N	Right	15	1.645	122	45.08
128	No		M	27	Caucasian	Y	Right	20	1.76	95	30.67
129	Yes	2	F	20	Caucasian	N	Right	15	1.62	67	25.53
130	Yes	2	F	20	Caucasian	N	Left	15	1.72	76	25.69
131	No		M	20	Caucasian	Y	Right	12	1.865	95	27.31
132	Yes	10	F	21	Caucasian	N	Right	16	1.8	79	24.38
133	Yes	10	F	20	Caucasian	Y	Right	15	1.78	89	28.09
134	No		M	21	Mixed	N	Right	15	1.675	74.87	26.63
135	No		F	19	Caucasian	Y	Left	15	1.803	74.4	22.89

Appendix 2.2 Chapter 2 study participant health screen and demographic overview.

Characteristic	Type	Count	Mean	SD
Sex	Female	114		
	Male	16		
Smoker	Female	27		
	Male	2		
Cigarettes Per Day			8.35	4.38
Ethnicity	Caucasian	93		
	Black	20		
	Oriental	0		
	Mixed	5		
	Other	12		
Handedness	Righthanded	117		
	Lefthanded	13		
Glasses or Lenses	No	77		
	Yes	53		
Age			22.59	6.38
Education Years			15.3	1.24
Height in Metres			1.67	0.08
Weight in Kgs			74.87	19.4
Body Mass Index (BMI)			26.63	6.38

3 Appendices

Appendix 3.1 Chapter 3 study participant health screen and demographic data.

Participant	Meds	Smoker	Sex	Age	Ethnicity	Glasses or Lenses	Handedness	Education Years	Height (metres)	Weight (Kgs)	BMI
2	No	No	Male	21	Caucasian	No	Right	15	1.79	102	31.83
4	No	No	Female	20	Caucasian	Yes	Right	15	1.71	76	25.99
5	No	No	Female	19	Black	No	Right	15	1.685	115	40.50
7	No	No	Female	19	Caucasian	No	Right	13	1.67	66	23.67
8	No	No	Male	20	Caucasian	No	Right	15	1.84	81	23.92
9	No	No	Female	23	Mixed	No	Right		1.66	75	27.22
10	No	No	Male	19	Mixed	Yes	Right	15	1.73	56	18.71
11	No	No	Female	20	Caucasian	Yes	Right	16	1.63	90	33.87
15	No	No	Male	20	Caucasian	Yes	Right	15	1.74	60	19.82
16	No	No	Female	19	Caucasian	No	Right	15	1.63	52	19.57
19	No	No	Female	20	Caucasian	Yes	Left	15	1.71	84	28.73
22	No	No	Male	24	Caucasian	No	Right	16	1.73	70	23.39
23	No	No	Female	21	Black	Yes	Right	14	1.57	57	23.12
24	No	No	Male	23	Other	Yes	Right	15	1.66	60	21.77
25	No	No	Female	19	Mixed	No	Right	15	1.61	51	19.68
26	No	No	Female	20	Black	Yes	Right	15	1.63	56	21.08
34	No	No	Female	20	Caucasian	Yes	Right	16	1.69	54	18.91
35	No	No	Male	27	Caucasian	No	Right	15	1.77	82	26.17
36	No	No	Male	20	Caucasian	Yes	Right	15	1.77	92	29.37
38	No	No	Female	22	Black	No	Right	15	1.58	63	25.24
39	No	No	Female	19	Caucasian	No	Right	15	1.7	72	24.91
40	No	No	Female	20	Caucasian	No	Right	15	1.56	52	21.37
41	No	No	Female	19	Caucasian	No	Right	15	1.74	112	36.99
42	No	No	Female	20	Other	Yes	Right	15	1.63	54	20.32
45	No	No	Female	20	Caucasian	Yes	Right	16	1.6	54	21.09
46	No	No	Female	19	Caucasian	Yes	Right	15	1.76	128	41.32
47	No	No	Male	19	Caucasian	Yes	Right	16	1.88	65	18.39
49	No	No	Female	20	Caucasian	No	Right	15	1.73	80	26.73
50	No	No	Female	19	Black	No	Left	15	1.64	58	21.56
51	No	No	Female	20	Caucasian	Yes	Right	15	1.75	66	21.55
52	No	No	Female	19	Caucasian	No	Right	15	1.73	85	28.40
53	No	No	Female	23	Caucasian	No	Right	15	1.66	66	23.95
54	No	No	Male	23	Caucasian	No	Right	16	1.74	77	25.43
55	No	No	Female	27	Caucasian	No	Right	15	1.76	77	24.86
57	No	No	Female	20	Caucasian	No	Right	15	1.67	77	27.61
59	No	No	Female	19	Caucasian	Yes	Right	15	1.75	69	22.53
62	No	No	Female	21	Black	Yes	Right	15	1.78	109	34.40
65	No	No	Female	20	Black	Yes	Right	15	1.56	65	26.71
66	No	No	Female	20	Black	No	Right	15	1.55	62	25.81
68	No	No	Female	20	Caucasian	Yes	Right	15	1.65	51	18.73
69	No	No	Female	20	Caucasian	No	Right	15	1.58	72	28.84
70	No	No	Female	19	Caucasian	Yes	Right	15	1.72	66	22.31
71	No	No	Female	21	Caucasian	Yes	Right	15	1.62	96	36.58

Continued

Participant	Meds	Smoker	Sex	Age	Ethnicity	Glasses or Lenses	Handedness	Education Years	Height (metres)	Weight (Kgs)	BMI
72	No	No	Female	19	Caucasian	Yes	Right	15	1.63	65	24.46
73	No	No	Female	34	Caucasian	No	Left	17	1.59	60	23.73
75	No	No	Female	27	Other	No	Right	16	1.66	59	21.41
80	No	No	Female	20	Caucasian	No	Right	15	1.61	76	29.32
81	No	No	Female	21	Caucasian	Yes	Right	15	1.62	42	16.00
82	No	No	Female	21	Black	No	Right	16	1.6	60	23.44
83	No	No	Female	20	Caucasian	No	Right	16	1.55	47	19.56
84	No	No	Female	24	Black	No	Right	15	1.67	55	19.72
86	No	No	Female	19	Caucasian	Yes	Right	15	1.73	62	20.72
91	No	No	Female	20	Caucasian	Yes	Left	15	1.62	60	22.86
92	No	No	Female	32	Black	No	Right	16	1.67	81	29.04
94	No	No	Female	22	Black	No	Right	15	1.65	45	16.53
95	No	No	Female	20	Black	Yes	Right	15	1.64	75	27.89
98	No	No	Female	21	Caucasian	Yes	Right	16	1.57	52	21.10
102	No	No	Female	21	Caucasian	Yes	Right	15	1.71	64	21.89
104	No	No	Female	19	Caucasian	Yes	Right	15	1.55	52	21.64
105	No	No	Male	20	Caucasian	No	Left	15	1.75	80	26.12
106	No	No	Male	22	Caucasian	No	Right	15	1.8	76	23.46
109	No	No	Female	19	Caucasian	Yes	Right	15	1.71	61	20.86
110	No	No	Female	19	Caucasian	No	Right	15	1.72	75	25.35
111	No	No	Male	20	Caucasian	No	Right	16	1.75	72	23.51
113	No	No	Female	33	Caucasian	Yes	Right	15	1.5	61	27.11
115	No	No	Female	20	Caucasian	No	Right	16	1.78	59	18.62
116	No	No	Female	19	Caucasian	Yes	Right	16	1.71	42	14.36
117	No	No	Female	20	Caucasian	No	Left	15	1.63	57	21.45
118	No	No	Female	20	Mixed	No	Right	15	1.59	75	29.67
119	No	No	Female	19	Caucasian	Yes	Right	15	1.62	63	24.01
121	No	No	Female	19	Caucasian	Yes	Right	15	1.78	63	19.88
122	No	No	Female	33	Caucasian	No	Right	15	1.6	66	25.78
125	No	No	Male	20	Caucasian	Yes	Right	15	1.81	118	36.02
126	No	No	Male	19	Other	Yes	Right	15	1.85	100	29.22
128	No	No	Female	23	Caucasian	No	Right	16	1.65	62	22.77
130	No	No	Female	21	Caucasian	Yes	Right	15	1.62	59	22.48
132	No	No	Female	21	Black	No	Right	16	1.71	95	32.49
134	No	No	Female	29	Caucasian	No	Right	14	1.65	70	25.71
137	No	No	Male	22	Caucasian	No	Right	13	1.73	73	24.39
138	No	No	Female	21	Caucasian	Yes	Right	16	1.82	65	19.62
139	No	No	Female	19	Caucasian	Yes	Right	15	1.63	50	18.82
140	No	No	Female	20	Caucasian	No	Right	15	1.72	100	33.80
141	No	No	Female	20	Caucasian	No	Right	16	1.73	58	19.38
142	No	No	Female	21	Other	Yes	Right	15	1.64	62	23.05
144	No	No	Female	30	Caucasian	Yes	Right	18	1.61	47	18.13
147	No	No	Female	20	Caucasian	Yes	Right	15	1.64	44	16.36
150	No	No	Male	22	Caucasian	No	Right	16	1.85	82	23.96
151	No	No	Male	23	Caucasian	Yes	Right	15	1.61	65	25.08
152	No	No	Female	23	Black	Yes	Right	15	1.63	73	27.48
155	No	No	Female	20	Caucasian	Yes	Right	15	1.53	95	40.58
158	No	No	Female	19	Other	No	Right	15	1.69	110	38.51
159	No	No	Female	21	Caucasian	No	Right	16	1.6	63	24.61

Appendix 3.2 Chapter 3 study participant health screen and demographic overview.

Characteristic	Type	Count	Mean	SD
Sex	Male	18		
	Female	74		
Ethnicity	Caucasian	67		
	Black	15		
	Oriental	0		
	Mixed	4		
	Other	6		
Handedness	Righthanded	85		
	Lefthanded	6		
Glasses or Lenses	No	45		
	Yes	45		
Age			21.30	3.32
Education Years			15.21	0.66
Height in Metres			1.68	0.08
Weight in Kgs			70.12	18.10
Body Mass Index (BMI)			24.84	5.70

Appendix 3.3 Word Recognition Old/New Accuracy. Means, SEMs of the four-way treatment x time x word type x valence mixed factorial ANOVA. Significant effects and interactions are indicated (Tr =Treatment, Ti = Time, WdTyp = Word Type, Val = Valence, WdTyp = Word Type. (*p<0.05), **p<0.005, ***P<0.001)

Outcome	Treatment	N	Word Type	Valence	Baseline			Post-Tests			Significant Effects and Interactions
					Mean	±	SEM	Mean	±	SEM	
Accuracy	Robinson's Sugar Free & Glucose	11	Old Word	Negative	73.03	±	5.71	53.03	±	5.51	
				Neutral	68.49	±	6.51	54.24	±	7.27	
				Positive	64.55	±	5.89	50.61	±	6.31	
			New Word	Negative	84.24	±	4.11	84.55	±	3.65	
				Neutral	95.15	±	2.80	91.52	±	2.70	
				Positive	85.46	±	4.40	89.40	±	3.60	
	Robinson's Sugar Free & Saccharin	9	Old Word	Negative	64.81	±	6.31	61.85	±	6.09	
				Neutral	64.81	±	7.20	58.52	±	8.03	
				Positive	60.74	±	6.51	58.15	±	6.97	
			New Word	Negative	89.26	±	4.55	92.59	±	4.03	
				Neutral	97.41	±	3.10	97.04	±	2.98	
				Positive	94.07	±	4.87	95.56	±	3.98	
	Robinson's Sugar Free & Aspartame	19	Old Word	Negative	60.00	±	4.34	48.60	±	4.19	
				Neutral	58.60	±	4.96	52.46	±	5.53	Ti *
				Positive	56.49	±	4.48	53.68	±	4.80	
			New Word	Negative	86.14	±	3.13	91.40	±	2.77	
				Neutral	94.39	±	2.13	95.97	±	2.05	WdTyp ***
				Positive	87.37	±	3.35	92.28	±	2.74	
	Lemon Juice & Glucose	12	Old Word	Negative	73.89	±	5.46	55.56	±	5.27	
				Neutral	68.89	±	6.24	57.78	±	6.96	Val ***
				Positive	63.06	±	5.64	61.67	±	6.04	
			New Word	Negative	86.67	±	3.94	91.94	±	3.49	
				Neutral	94.72	±	2.68	96.95	±	2.58	Ti x WdTyp ***
				Positive	87.22	±	4.21	93.89	±	3.44	
	Lemon Juice & Saccharin	10	Old Word	Negative	69.00	±	5.99	63.67	±	5.77	
				Neutral	67.67	±	6.83	53.00	±	7.62	Ti x Val ***
				Positive	64.67	±	6.18	62.67	±	6.61	
			New Word	Negative	81.00	±	4.31	85.33	±	3.82	WdTyp x Val ***
				Neutral	92.33	±	2.94	93.67	±	2.83	
				Positive	77.00	±	4.62	88.00	±	3.77	
	Lemon Juice & Aspartame	12	Old Word	Negative	70.56	±	5.46	63.61	±	5.27	Ti x WdTyp x Val *
				Neutral	64.45	±	6.24	66.67	±	6.96	
				Positive	65.28	±	5.64	66.39	±	6.04	
			New Word	Negative	83.61	±	3.94	88.33	±	3.49	
				Neutral	91.67	±	2.68	93.33	±	2.58	
				Positive	85.28	±	4.21	89.45	±	3.44	
	Water	12	Old Word	Negative	61.11	±	5.46	54.17	±	5.27	
				Neutral	56.95	±	6.24	49.17	±	6.96	
				Positive	54.17	±	5.64	49.44	±	6.04	
			New Word	Negative	79.45	±	3.94	81.94	±	3.49	
				Neutral	88.61	±	2.68	89.72	±	2.58	
				Positive	78.89	±	4.21	82.78	±	3.44	

Appendix 3.4 Word Recognition Old/New response reaction time Means, SEMs for the four-way treatment x time x word type x valence mixed factorial ANOVA. Significant effects and interactions are indicated (Tr =Treatment, Ti = Time, WdTyp = Word Type, Val = Valence, WdTyp = Word Type; (*p<0.05), **p<0.005, ***P<0.001)

Outcome	Treatment	N	Word Type	Valence	Baseline			Post-Tests			Significant Effects and Interactions
					Mean	±	SEM	Mean	±	SEM	
Response Reaction Speed	Robinson's Sugar Free & Glucose	11	Old Word	Negative	1639.83	±	124.52	1425.68	±	103.39	
				Neutral	1541.27	±	131.57	1254.08	±	107.45	
				Positive	1573.94	±	142.40	1413.96	±	99.87	
			New Word	Negative	1250.72	±	104.34	996.17	±	68.45	
				Neutral	1176.79	±	94.04	919.61	±	68.09	
				Positive	1300.11	±	107.75	1021.66	±	88.14	
	Robinson's Sugar Free & Saccharin	9	Old Word	Negative	1417.62	±	137.66	1237.80	±	114.30	
				Neutral	1293.20	±	145.46	1169.40	±	118.79	
				Positive	1441.11	±	157.43	1105.64	±	110.41	
			New Word	Negative	1211.92	±	115.35	952.36	±	75.67	
				Neutral	1095.02	±	103.97	895.27	±	75.28	
				Positive	1233.28	±	119.13	991.03	±	97.45	
	Robinson's Sugar Free & Aspartame	19	Old Word	Negative	1476.97	±	94.75	1345.67	±	78.67	
				Neutral	1483.94	±	100.11	1306.06	±	81.76	Ti ***
				Positive	1528.83	±	108.35	1247.09	±	75.99	
			New Word	Negative	1178.43	±	79.39	926.67	±	52.08	
				Neutral	1016.09	±	71.56	889.58	±	51.81	WdTyp ***
				Positive	1240.34	±	81.99	937.43	±	67.07	
	Lemon Juice & Glucose	12	Old Word	Negative	1631.52	±	119.22	1442.75	±	98.98	
				Neutral	1539.50	±	125.97	1266.00	±	102.88	Val ***
				Positive	1711.87	±	136.34	1293.76	±	95.62	
			New Word	Negative	1433.97	±	99.89	1209.39	±	65.53	
				Neutral	1237.49	±	90.04	989.03	±	65.19	WdTyp x Val *
				Positive	1473.34	±	103.17	1142.94	±	84.39	
	Lemon Juice & Saccharin	10	Old Word	Negative	1372.34	±	130.60	1145.23	±	108.43	
				Neutral	1406.77	±	138.00	1076.94	±	112.70	Ti x WdTyp x Val *
				Positive	1430.49	±	149.35	1090.56	±	104.74	
			New Word	Negative	1253.50	±	109.43	984.50	±	71.79	
				Neutral	1110.16	±	98.63	919.46	±	71.41	
				Positive	1215.09	±	113.01	1006.02	±	92.45	
	Lemon Juice & Aspartame	12	Old Word	Negative	1585.53	±	119.22	1213.34	±	98.98	
				Neutral	1409.73	±	125.97	1129.75	±	102.88	
				Positive	1497.04	±	136.34	1135.15	±	95.62	
			New Word	Negative	1412.02	±	99.89	979.92	±	65.53	
				Neutral	1109.67	±	90.04	930.58	±	65.19	
				Positive	1290.92	±	103.17	995.21	±	84.39	
	Water	12	Old Word	Negative	1427.56	±	119.22	1217.09	±	98.98	
				Neutral	1418.40	±	125.97	1183.60	±	102.88	
				Positive	1356.94	±	136.34	1210.72	±	95.62	
			New Word	Negative	1292.44	±	99.89	963.98	±	65.53	
				Neutral	1192.97	±	90.04	948.48	±	65.19	
				Positive	1261.54	±	103.17	1022.95	±	84.39	

Appendix 3.5 Word Recognition Recollection/Familiarity subjective judgements. Means, SEMs for the four-way treatment x time x word type x valence mixed factorial ANOVA. Significant effects and interactions are indicated (Tr =Treatment, Ti = Time, RecTyp = Recognition Type, Val = Valence, (*p<0.05), **p<0.005, ***P<0.001)

Outcome	Treatment	N	Recognition Type	Valence	Baseline			Post-Tests			Significant Effects and Interactions
					Mean	±	SEM	Mean	±	SEM	
% of Correct Recognitions	Robinson's Sugar Free & Glucose	11	Recollection	Negative	32.23	±	2.78	30.28	±	2.76	
				Neutral	30.34	±	2.79	30.96	±	3.24	
				Positive	28.35	±	3.31	29.67	±	3.22	
			Familiarity	Negative	35.25	±	5.74	39.10	±	6.39	
				Neutral	22.71	±	5.91	28.88	±	6.07	
				Positive	32.94	±	5.11	22.12	±	6.25	
	Robinson's Sugar Free & Saccharin	9	Recollection	Negative	32.78	±	3.07	30.24	±	3.05	
				Neutral	32.47	±	3.08	31.83	±	3.58	
				Positive	34.74	±	3.66	37.93	±	3.56	
			Familiarity	Negative	33.04	±	6.35	52.24	±	7.07	
				Neutral	29.23	±	6.54	24.42	±	6.71	
				Positive	37.73	±	5.65	23.34	±	6.91	
	Robinson's Sugar Free & Aspartame	19	Recollection	Negative	33.00	±	2.11	28.42	±	2.10	
				Neutral	32.95	±	2.12	33.76	±	2.47	**Ti ***
				Positive	34.06	±	2.52	37.82	±	2.45	
			Familiarity	Negative	39.14	±	4.37	33.55	±	4.87	**Val ***
				Neutral	32.17	±	4.50	25.32	±	4.62	
				Positive	28.47	±	3.89	35.87	±	4.76	
	Lemon Juice & Glucose	12	Recollection	Negative	36.48	±	2.66	27.93	±	2.64	**Ti x RecTyp ***
				Neutral	34.99	±	2.67	30.90	±	3.10	
				Positive	28.53	±	3.17	41.17	±	3.08	**RecTyp x Val ***
			Familiarity	Negative	30.66	±	5.50	34.47	±	6.12	
				Neutral	34.34	±	5.66	24.93	±	5.81	**Ti Val x Tr ***
				Positive	34.99	±	4.89	23.93	±	5.99	
	Lemon Juice & Saccharin	10	Recollection	Negative	34.06	±	2.91	37.16	±	2.89	
				Neutral	35.36	±	2.93	28.44	±	3.40	**Ti x RecTyp x Val ***
				Positive	30.59	±	3.47	34.40	±	3.37	
			Familiarity	Negative	29.68	±	6.02	35.15	±	6.71	
				Neutral	31.69	±	6.20	15.65	±	6.36	
				Positive	38.63	±	5.36	29.20	±	6.56	
	Lemon Juice & Aspartame	12	Recollection	Negative	35.45	±	2.66	31.54	±	2.64	
				Neutral	32.38	±	2.67	34.82	±	3.10	
				Positive	32.17	±	3.17	33.65	±	3.08	
			Familiarity	Negative	49.37	±	5.50	24.75	±	6.12	
				Neutral	22.69	±	5.66	26.01	±	5.81	
				Positive	27.94	±	4.89	23.37	±	5.99	
	Water	12	Recollection	Negative	30.48	±	2.66	29.07	±	2.64	
				Neutral	30.30	±	2.67	27.10	±	3.10	
				Positive	30.89	±	3.17	35.50	±	3.08	
			Familiarity	Negative	33.54	±	5.50	39.23	±	6.12	
				Neutral	35.33	±	5.66	32.99	±	5.81	
				Positive	31.14	±	4.89	27.78	±	5.99	

Appendix 3.6 Picture Recognition Old/New Accuracy. Means, SEMs for the four-way treatment x time x picture type x valence mixed factorial ANOVA. Significant effects and interactions are indicated (Tr =Treatment, Ti = Time, PicTyp = Picture Type, Val = Valence; (*p<0.05), **p<0.005, ***P<0.001)

Outcome	Treatment	N	Picture Type	Valence	Baseline			Post-Tests			Significant Effects and Interactions
					Mean	±	SEM	Mean	±	SEM	
Accuracy	Robinson's Sugar Free & Glucose	11	Old Picture	Negative	47.55	±	3.43	81.12	±	5.77	
				Neutral	50.35	±	3.83	81.12	±	6.10	
				Positive	48.95	±	5.16	71.33	±	5.74	
			New Picture	Negative	61.54	±	3.69	95.11	±	2.59	
				Neutral	59.44	±	3.48	95.81	±	2.15	
				Positive	67.83	±	3.92	87.42	±	3.28	
	Robinson's Sugar Free & Saccharin	11	Old Picture	Negative	43.36	±	3.43	79.02	±	5.77	
				Neutral	52.45	±	3.83	80.42	±	6.10	
				Positive	48.95	±	5.16	79.72	±	5.74	
			New Picture	Negative	58.74	±	3.69	99.30	±	2.59	
				Neutral	57.35	±	3.48	99.30	±	2.15	
				Positive	60.84	±	3.92	95.81	±	3.28	
	Robinson's Sugar Free & Aspartame	18	Old Picture	Negative	42.73	±	2.68	76.50	±	4.51	
				Neutral	52.14	±	2.99	76.07	±	4.77	**Ti *****
				Positive	50.00	±	4.03	78.63	±	4.49	
			New Picture	Negative	53.85	±	2.88	95.30	±	2.03	
				Neutral	58.12	±	2.72	96.16	±	1.68	**PicTyp *****
				Positive	65.81	±	3.07	94.02	±	2.57	
	Lemon Juice & Glucose	13	Old Picture	Negative	52.66	±	3.16	76.33	±	5.31	
				Neutral	47.93	±	3.52	82.84	±	5.61	**Val ****
				Positive	49.11	±	4.75	77.52	±	5.28	
			New Picture	Negative	54.44	±	3.39	98.23	±	2.38	
				Neutral	62.13	±	3.20	95.27	±	1.97	**Ti x PicTyp *****
				Positive	60.95	±	3.61	94.08	±	3.02	
	Lemon Juice & Saccharin	10	Old Picture	Negative	43.85	±	3.60	79.23	±	6.06	
				Neutral	52.31	±	4.01	80.77	±	6.40	**Ti x Val ****
				Positive	50.00	±	5.41	76.16	±	6.02	
			New Picture	Negative	56.92	±	3.87	94.62	±	2.72	**Ti x PicTyp x Val ***
				Neutral	63.08	±	3.65	95.39	±	2.25	
				Positive	54.62	±	4.11	89.23	±	3.44	
	Lemon Juice & Aspartame	14	Old Picture	Negative	50.55	±	3.04	78.57	±	5.12	
				Neutral	54.40	±	3.39	78.57	±	5.41	
				Positive	49.45	±	4.57	78.57	±	5.09	
			New Picture	Negative	59.34	±	3.27	92.31	±	2.30	
				Neutral	55.49	±	3.08	92.86	±	1.90	
				Positive	56.04	±	3.48	86.27	±	2.91	
	Water	12	Old Picture	Negative	47.43	±	3.29	73.72	±	5.53	
				Neutral	57.05	±	3.66	80.13	±	5.84	
				Positive	45.51	±	4.94	78.85	±	5.50	
			New Picture	Negative	56.41	±	3.53	94.23	±	2.48	
				Neutral	55.77	±	3.33	93.59	±	2.06	
				Positive	60.90	±	3.76	89.10	±	3.14	

Appendix 3.7 Flanker task accuracy analysis. Means, SEM for the four-way treatment x time x congruency x direction mixed factorial ANOVA. Significant effects and interactions are indicated (Ti = Time, Tr =Treatment, Cong = Congruency, Dir = Direction) (*p<0.05, **p<0.005, ***P<0.001)

Treatment	Congruency	Direction	N	Baseline			Post-Tests			Significant Effects and Interactions
				Mean	±	SEM	Mean	±	SEM	
Robinson's Sugar Free & Glucose	Congruent	left	12	99.13	±	2.06	97.93	±	1.03	
		Right	12	98.17	±	1.53	97.91	±	1.85	
	Incongruent	Left	12	95.83	±	5.13	93.88	±	4.14	
		Right	12	96.23	±	4.73	93.68	±	4.21	
	Neutral	left	12	97.77	±	2.04	97.69	±	1.25	
		Right	12	98.00	±	1.25	97.15	±	1.72	
	No/Go	Left	12	73.05	±	7.61	73.52	±	7.03	
		Right	12	73.58	±	7.81	69.47	±	7.14	
Robinson's Sugar Free & Saccharin	Congruent	left	12	97.45	±	2.06	97.22	±	1.03	
		Right	12	96.69	±	1.53	96.68	±	1.85	
	Incongruent	Left	12	91.83	±	5.13	90.90	±	4.14	
		Right	12	91.85	±	4.73	90.45	±	4.21	
	Neutral	left	12	95.96	±	2.04	96.63	±	1.25	Cong ***
		Right	12	98.23	±	1.25	98.66	±	1.72	
	No/Go	Left	12	88.27	±	7.61	86.89	±	7.03	Ti x Dir *
		Right	12	86.68	±	7.81	86.46	±	7.14	
Robinson's Sugar Free & Aspartame	Congruent	left	19	97.73	±	1.64	99.70	±	0.82	
		Right	19	98.75	±	1.22	99.40	±	1.47	
	Incongruent	Left	19	90.51	±	4.08	90.99	±	3.29	
		Right	19	92.22	±	3.76	91.46	±	3.35	
	Neutral	left	19	97.37	±	1.62	99.56	±	0.99	
		Right	19	98.73	±	0.99	98.69	±	1.36	
	No/Go	Left	19	89.94	±	6.05	92.13	±	5.59	
		Right	19	88.24	±	6.20	88.07	±	5.68	
Lemon Juice & Glucose	Congruent	left	12	99.56	±	2.06	99.34	±	1.03	
		Right	12	100.00	±	1.53	98.90	±	1.85	
	Incongruent	Left	12	89.22	±	5.13	93.70	±	4.14	
		Right	12	89.04	±	4.73	93.10	±	4.21	
	Neutral	left	12	99.12	±	2.04	99.31	±	1.25	
		Right	12	99.55	±	1.25	99.77	±	1.72	
	No/Go	Left	12	92.27	±	7.61	91.90	±	7.03	
		Right	12	90.18	±	7.81	88.86	±	7.14	
Lemon Juice & Saccharin	Congruent	left	10	97.35	±	2.26	98.37	±	1.13	
		Right	10	97.64	±	1.68	91.53	±	2.03	
	Incongruent	Left	10	94.89	±	5.62	91.46	±	4.54	
		Right	10	95.51	±	5.18	95.11	±	4.61	
	Neutral	left	10	98.08	±	2.24	98.12	±	1.37	
		Right	10	98.72	±	1.37	91.38	±	1.88	
	No/Go	Left	10	72.63	±	8.34	78.82	±	7.70	
		Right	10	73.64	±	8.55	74.76	±	7.82	
Lemon Juice & Aspartame	Congruent	left	13	98.56	±	1.98	98.12	±	0.99	
		Right	13	98.76	±	1.47	98.76	±	1.78	
	Incongruent	Left	13	94.20	±	4.93	94.44	±	3.98	
		Right	13	92.90	±	4.54	94.72	±	4.05	
	Neutral	left	13	97.95	±	1.96	98.13	±	1.20	
		Right	13	97.75	±	1.20	98.35	±	1.65	
	No/Go	Left	13	71.01	±	7.32	74.32	±	6.75	
		Right	13	72.02	±	7.50	73.26	±	6.86	
Water	Congruent	left	14	93.97	±	1.91	98.85	±	0.96	
		Right	14	96.33	±	1.42	99.61	±	1.71	
	Incongruent	Left	14	92.64	±	4.75	95.77	±	3.84	
		Right	14	94.00	±	4.38	96.45	±	3.90	
	Neutral	left	14	94.23	±	1.89	99.01	±	1.16	
		Right	14	96.43	±	1.16	97.46	±	1.59	
	No/Go	Left	14	73.92	±	7.05	77.52	±	6.51	
		Right	14	76.30	±	7.23	78.83	±	6.61	

Appendix 3.8 Flanker task response reaction time (milliseconds). Means, SEM for the four-way treatment x time x congruency x direction mixed factorial ANOVA. Significant effects and interactions are indicated (Ti = Time, Tr =Treatment, Cong = Congruency, Dir = Direction) (*p<0.05, **p<0.005, ***P<0.001)

Treatment	Congruency	Direction	N	Baseline			Post-Tests			Significant Effects and Interactions
				Mean	±	SEM	Mean	±	SEM	
Robinson's Sugar Free & Glucose	Congruent	left	12	534.49	±	19.00	519.89	±	18.27	
		Right	12	534.38	±	18.20	506.55	±	16.32	
	Incongruent	Left	12	584.24	±	21.59	564.14	±	19.92	
		Right	12	600.82	±	21.67	571.62	±	20.27	
	Neutral	left	12	541.35	±	20.11	522.48	±	20.14	
		Right	12	547.01	±	18.55	500.49	±	16.62	
Robinson's Sugar Free & Saccharin	Congruent	left	12	496.80	±	19.00	468.22	±	18.27	
		Right	12	503.32	±	18.20	472.39	±	16.32	
	Incongruent	Left	12	534.56	±	21.59	513.55	±	19.92	Ti***
		Right	12	529.29	±	21.67	511.90	±	20.27	
	Neutral	left	12	506.34	±	20.11	482.19	±	20.14	Cong ***
		Right	12	500.35	±	18.55	469.94	±	16.62	
Robinson's Sugar Free & Aspartame	Congruent	left	18	515.17	±	15.52	489.59	±	14.92	Dir**
		Right	18	503.98	±	14.86	488.26	±	13.32	
	Incongruent	Left	18	572.40	±	17.63	555.97	±	16.26	Ti x Dir *
		Right	18	578.40	±	17.70	559.34	±	16.55	
	Neutral	left	18	532.07	±	16.42	514.22	±	16.44	
		Right	18	523.18	±	15.14	496.27	±	13.57	
Lemon Juice & Glucose	Congruent	left	11	519.39	±	19.85	489.16	±	19.09	
		Right	11	496.21	±	19.01	474.04	±	17.04	
	Incongruent	Left	11	581.51	±	22.55	557.65	±	20.81	
		Right	11	564.98	±	22.64	540.35	±	21.17	
	Neutral	left	11	509.56	±	21.01	493.57	±	21.03	
		Right	11	507.20	±	19.37	481.43	±	17.36	
Lemon Juice & Saccharin	Congruent	left	10	507.75	±	20.82	491.92	±	20.02	
		Right	10	510.51	±	19.94	492.04	±	17.88	
	Incongruent	Left	10	572.51	±	23.65	544.53	±	21.82	
		Right	10	569.51	±	23.74	537.37	±	22.21	
	Neutral	left	10	515.22	±	22.03	506.75	±	22.06	
		Right	10	509.39	±	20.32	486.70	±	18.20	
Lemon Juice & Aspartame	Congruent	left	13	535.14	±	18.26	510.48	±	17.56	
		Right	13	533.03	±	17.49	491.74	±	15.68	
	Incongruent	Left	13	605.51	±	20.74	568.08	±	19.14	
		Right	13	602.05	±	20.82	560.00	±	19.48	
	Neutral	left	13	543.23	±	19.32	515.41	±	19.35	
		Right	13	529.77	±	17.82	493.33	±	15.97	
Water	Congruent	left	14	509.63	±	17.59	490.12	±	16.92	
		Right	14	515.48	±	16.85	486.62	±	15.11	
	Incongruent	Left	14	581.70	±	19.99	558.85	±	18.44	
		Right	14	569.18	±	20.07	554.96	±	18.77	
	Neutral	left	14	525.54	±	18.62	509.57	±	18.64	
		Right	14	524.64	±	17.17	497.43	±	15.39	

4 Appendices

Appendix 4.1 Chapter 4 Participant health screen and demographic data.

Participant	Smoker	Gender	Age	Ethnicity	Glasses/Lenses	Handed_ness	Educ_Years	Height (metres)	Weight (Kgs)	Waist (cms)	Hips (cms)	Waist/Hip ratio	BMI
2	No	Male	19	Caucasian	Yes	Right	15	1.89	63	76	94	0.8085	17.64
3	No	Male	21	Caucasian	No	Left	15	1.85	109	109	121	0.9008	31.85
4	No	Male	19	Caucasian	No	Right	15	1.78	72	88	100	0.88	22.72
7	No	Female	18	Caucasian	No	Right	14	1.75	74	80	95	0.8421	24.16
8	No	Female	19	Caucasian	No	Right	14	1.77	60	71.5	90	0.7944	19.15
10	No	Male	29	Caucasian	No	Right	15	1.77	87	92	105	0.8762	27.77
11	No	Female	19	Caucasian	Yes	Right	15	1.74	68	75	99	0.7576	22.46
13	No	Male	22	Caucasian	Yes	Right	15	1.78	87	91	102	0.8922	27.46
14	No	Female	24	Caucasian	No	Right	15	1.6	83	88	111	0.7928	32.42
15	No	Male	19	Caucasian	No	Left	14	1.78	85	99	107	0.9252	26.83
16	No	Female	18	Caucasian	Yes	Left	14	1.65	66	81	97	0.8351	24.24
17	No	Female	19	Caucasian	No	Left	14	1.66	68	65	81	0.8025	24.68
18	No	Female	19	Caucasian	Yes	Right	15	1.7	78	80	101	0.7921	26.99
19	No	Female	22	Caucasian	Yes	Right	15	1.71	72	84	105	0.8	24.62
20	No	Male	20	Caucasian	Yes	Right	11	1.8	68	81	94	0.8617	20.99
21	No	Female	31	Caucasian	Yes	Right	16	1.65	92	102	119	0.8571	33.79
22	No	Female	23	Caucasian	No	Right	13	1.65	62	76	93	0.8172	22.77
23	No	Female	20	Caucasian	Yes	Right	16	1.59	62	74	94	0.7872	24.52
24	No	Female	34	Asian	No	Right	15	1.63	75	82	106	0.7736	28.23
25	No	Male	19	Caucasian	No	Right	15	1.79	91	91	102	0.8922	28.40
26	No	Male	19	Caucasian	Yes	Right	15	1.93	75	83	98	0.8469	20.13

Appendix 4.2 Chapter 4 Participant health screen and demographic overview.

Characteristic	Type	Count	Mean	SD
Sex	Male	9		
	Female	12		
Ethnicity	Caucasian	20		
	Asian	1		
Handedness	Righthanded	17		
	Lefthanded	4		
Glasses or Lenses	No	11		
	Yes	10		
Age			21.57	4.46
Education Years			14.57	1.08
Height in Metres			1.74	0.09
Weight in Kgs			76.05	12.44
Waist in Cms			84.21	10.60
Hips in Cms			100.67	9.26
Body Mass Index (BMI)			25.32	4.28
Waist to Hip Ratio (WHR)			0.84	0.05

Appendix 4.3 Encoding phase P1 component in the 50 to 170 millisecond latency window. Means, SEMs for the five-way treatment x region x valence x hemisphere x glucoregulation mixed factorial ANOVA. Significant effects and interactions are indicated (Gluc = Glucoregulation, Tr =Treatment, Reg = Region, Hem = hemisphere, Val = Valence) (*p<0.05), **p<0.005, ***P<0.001)

Glucoregulation	Treatment	Region	Valence	Hemisphere	N	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	Glucose	Anterior	Negative	Left	11	-1.183	±	0.40	
				Midline	11	-1.292	±	0.51	
				Right	11	-1.175	±	0.56	
			Neutral	Left	11	-0.873	±	0.38	
				Midline	11	-1.223	±	0.52	
				Right	11	-1.03	±	0.62	
			Positive	Left	11	-1.055	±	0.36	
				Midline	11	-1.812	±	0.38	
				Right	11	-1.953	±	0.46	
		Posterior	Negative	Left	11	0.677	±	0.46	
				Midline	11	0.537	±	0.37	
				Right	11	1.343	±	0.43	
			Neutral	Left	11	1.345	±	0.47	
				Midline	11	1.485	±	0.41	
				Right	11	1.882	±	0.41	
			Positive	Left	11	1.029	±	0.49	
				Midline	11	0.978	±	0.50	
				Right	11	1.656	±	0.50	
	Placebo	Anterior	Negative	Left	11	-0.686	±	0.44	
				Midline	11	-1.214	±	0.44	
				Right	11	-0.94	±	0.39	
			Neutral	Left	11	-0.77	±	0.36	
				Midline	11	-1.121	±	0.56	
				Right	11	-0.973	±	0.41	
			Positive	Left	11	-0.036	±	0.57	
				Midline	11	-0.873	±	0.54	
				Right	11	-0.95	±	0.49	
		Posterior	Negative	Left	11	0.946	±	0.37	
				Midline	11	0.59	±	0.39	
				Right	11	1.653	±	0.37	
			Neutral	Left	11	1.003	±	0.33	Reg x Hem **
				Midline	11	1.608	±	0.36	
				Right	11	1.643	±	0.28	
			Positive	Left	11	0.37	±	0.60	Reg ***
				Midline	11	0.242	±	0.60	
				Right	11	1.057	±	0.48	Hem *
Poorer Regulators	Glucose	Anterior	Negative	Left	7	-1.128	±	0.50	
				Midline	7	-1.35	±	0.64	
				Right	7	-1.217	±	0.70	
			Neutral	Left	7	-0.879	±	0.47	
				Midline	7	-1.508	±	0.65	
				Right	7	-1.174	±	0.78	
			Positive	Left	7	-1.042	±	0.45	
				Midline	7	-0.685	±	0.48	
				Right	7	-0.735	±	0.57	
		Posterior	Negative	Left	7	1.461	±	0.57	
				Midline	7	1.182	±	0.47	
				Right	7	1.704	±	0.53	
			Neutral	Left	7	1.06	±	0.59	
				Midline	7	0.536	±	0.52	
				Right	7	1.568	±	0.51	
			Positive	Left	7	0.484	±	0.61	
				Midline	7	-0.093	±	0.62	
				Right	7	1.507	±	0.62	
	Placebo	Anterior	Negative	Left	7	-0.868	±	0.55	
				Midline	7	-1.386	±	0.55	
				Right	7	-0.927	±	0.48	
			Neutral	Left	7	-1.832	±	0.45	
				Midline	7	-2.114	±	0.70	
				Right	7	-1.515	±	0.51	
			Positive	Left	7	-1.793	±	0.72	
				Midline	7	-1.69	±	0.68	
				Right	7	-1.286	±	0.62	
		Posterior	Negative	Left	7	0.113	±	0.46	
				Midline	7	0.256	±	0.49	
				Right	7	2.178	±	0.46	
			Neutral	Left	7	1.049	±	0.41	
				Midline	7	0.442	±	0.45	
				Right	7	1.622	±	0.36	
			Positive	Left	7	1.163	±	0.76	
				Midline	7	0.797	±	0.75	
				Right	7	2.252	±	0.60	

Appendix 4.4 Encoding Phase N1 Component in the 165 to 220 millisecond latency window. Means, SEMs for the five-way treatment x region x valence x hemisphere x glucoregulation mixed factorial ANOVA. Significant effects and interactions are indicated (Gluc = Glucoregulation, Tr =Treatment, Reg = Region, Hem =Hemisphere, Val = Valence) ($p<.05$).**

Glucoregulation	Treatment	Region	Valence	Hemisphere	N	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	Glucose	Anterior	Negative	Left	11	2.371	±	0.71	
				Midline	11	1.897	±	0.72	
				Right	11	1.282	±	0.82	
			Neutral	Left	11	1.744	±	0.74	
				Midline	11	1.691	±	0.74	
				Right	11	1.672	±	0.81	
			Positive	Left	11	1.682	±	0.77	
				Midline	11	1.224	±	0.81	
				Right	11	0.345	±	0.84	
		Posterior	Negative	Left	11	-1.112	±	0.84	
				Midline	11	-1.705	±	0.68	
				Right	11	-0.645	±	0.73	
			Neutral	Left	11	-0.434	±	0.79	
				Midline	11	-1.144	±	0.65	
				Right	11	0.144	±	0.93	
			Positive	Left	11	-0.736	±	1.02	
				Midline	11	-1.044	±	0.73	
				Right	11	0.09	±	0.92	
	Placebo	Anterior	Negative	Left	11	2.293	±	0.74	
				Midline	11	1.952	±	0.74	
				Right	11	1.465	±	0.71	
			Neutral	Left	11	2.09	±	0.62	
				Midline	11	1.758	±	0.67	
				Right	11	1.55	±	0.64	
			Positive	Left	11	3.089	±	0.89	
				Midline	11	2.248	±	0.86	
				Right	11	1.279	±	0.65	
		Posterior	Negative	Left	11	-0.436	±	0.61	
				Midline	11	-0.989	±	0.61	
				Right	11	-0.604	±	0.86	
			Neutral	Left	11	-0.542	±	0.61	Reg x Hem **
				Midline	11	-0.826	±	0.64	
				Right	11	-0.36	±	0.85	
			Positive	Left	11	-0.78	±	0.74	
				Midline	11	-1.165	±	0.80	
				Right	11	-0.855	±	0.88	
Poorer Regulators	Glucose	Anterior	Negative	Left	7	1.169	±	0.89	
				Midline	7	1.226	±	0.91	
				Right	7	0.503	±	1.02	
			Neutral	Left	7	0.807	±	0.93	
				Midline	7	-0.009	±	0.93	
				Right	7	-0.288	±	1.01	
			Positive	Left	7	1.115	±	0.97	
				Midline	7	0.892	±	1.01	
				Right	7	0.145	±	1.05	
		Posterior	Negative	Left	7	0.184	±	1.05	
				Midline	7	-1.178	±	0.86	
				Right	7	-0.329	±	0.91	
			Neutral	Left	7	0.476	±	0.99	
				Midline	7	-0.635	±	0.81	
				Right	7	0.039	±	1.17	
			Positive	Left	7	-0.54	±	1.27	
				Midline	7	-2.076	±	0.92	
				Right	7	-0.514	±	1.15	
	Placebo	Anterior	Negative	Left	7	1.265	±	0.92	
				Midline	7	0.881	±	0.92	
				Right	7	0.657	±	0.89	
			Neutral	Left	7	-0.564	±	0.77	
				Midline	7	-0.456	±	0.84	
				Right	7	0.328	±	0.81	
			Positive	Left	7	0.176	±	1.12	
				Midline	7	0.385	±	1.07	
				Right	7	0.029	±	0.82	
		Posterior	Negative	Left	7	-1.592	±	0.76	
				Midline	7	-2.079	±	0.77	
				Right	7	-0.515	±	1.08	
			Neutral	Left	7	1.042	±	0.77	
				Midline	7	-0.192	±	0.81	
				Right	7	0.081	±	1.07	
			Positive	Left	7	0.141	±	0.92	
				Midline	7	-0.434	±	1.01	
				Right	7	0.278	±	1.10	

Appendix 4.5 Encoding Phase P3 Component in the 300 to 500 millisecond latency window. Means, SEMs for the via the five-way treatment x region x valence x hemisphere x glucoregulation mixed factorial ANOVA. Significant effects and interactions are indicated (Gluc = Glucoregulation, Tr =Treatment, Reg = Region, Hem = Hemisphere, Val = Valence) (*p<0.05), **p<0.005, ***P<0.001)

Glucoregulation	Treatment	Region	Valence	Hemisphere	N	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	Glucose	Anterior	Negative	Left	11	-0.521	±	0.59	
				Midline	11	-1.148	±	0.69	
				Right	11	-1.096	±	0.68	
			Neutral	Left	11	-1.798	±	0.74	
				Midline	11	-2.096	±	0.89	
				Right	11	-0.74	±	0.65	
			Positive	Left	11	-0.964	±	0.46	
				Midline	11	-0.757	±	0.61	
				Right	11	-0.964	±	0.71	
		Posterior	Negative	Left	11	0.932	±	0.67	
				Midline	11	0.454	±	0.68	
				Right	11	1.247	±	0.54	
			Neutral	Left	11	1.502	±	0.55	
				Midline	11	0.736	±	0.55	
				Right	11	2.016	±	0.59	
			Positive	Left	11	0.841	±	0.48	
				Midline	11	0.655	±	0.42	
				Right	11	1.312	±	0.55	
	Placebo	Anterior	Negative	Left	11	0.519	±	0.73	
				Midline	11	0.08	±	0.87	
				Right	11	-0.162	±	0.58	
			Neutral	Left	11	0.186	±	0.70	
				Midline	11	-0.518	±	0.64	
				Right	11	0.271	±	0.60	
			Positive	Left	11	1.867	±	1.02	
				Midline	11	-0.184	±	0.59	
				Right	11	-0.716	±	0.63	
		Posterior	Negative	Left	11	0.922	±	0.50	
				Midline	11	-0.05	±	0.54	
				Right	11	1.356	±	0.52	
			Neutral	Left	11	0.376	±	0.66	Gluc xTr x Reg x Hem *
				Midline	11	-0.469	±	0.76	
				Right	11	0.324	±	0.80	
			Positive	Left	11	0.442	±	0.58	
				Midline	11	-0.236	±	0.74	Val x Reg xHem **
				Right	11	0.604	±	0.75	
Poorer Regulators	Glucose	Anterior	Negative	Left	7	-0.492	±	0.74	
				Midline	7	-0.577	±	0.86	Reg x Hem *
				Right	7	-0.528	±	0.86	
			Neutral	Left	7	-1.702	±	0.93	Reg *
				Midline	7	-1.968	±	1.11	
				Right	7	-0.903	±	0.81	Hem **
			Positive	Left	7	-1.525	±	0.57	
				Midline	7	-2.193	±	0.77	
				Right	7	-1.867	±	0.89	
		Posterior	Negative	Left	7	0.194	±	0.84	
				Midline	7	-0.733	±	0.86	
				Right	7	1.425	±	0.68	
			Neutral	Left	7	1.012	±	0.69	
				Midline	7	-0.607	±	0.68	
				Right	7	1.948	±	0.74	
			Positive	Left	7	0.144	±	0.60	
				Midline	7	-1.059	±	0.52	
				Right	7	1.773	±	0.69	
	Placebo	Anterior	Negative	Left	7	-0.564	±	0.91	
				Midline	7	-1.135	±	1.09	
				Right	7	-0.901	±	0.72	
			Neutral	Left	7	-2.267	±	0.87	
				Midline	7	-2.811	±	0.80	
				Right	7	-0.658	±	0.75	
			Positive	Left	7	-1.785	±	1.28	
				Midline	7	-1.978	±	0.74	
				Right	7	-1.245	±	0.79	
		Posterior	Negative	Left	7	0.273	±	0.63	
				Midline	7	-0.209	±	0.67	
				Right	7	1.802	±	0.65	
			Neutral	Left	7	1.268	±	0.82	
				Midline	7	-0.787	±	0.96	
				Right	7	1.173	±	1.01	
			Positive	Left	7	1.842	±	0.72	
				Midline	7	0.53	±	0.93	
				Right	7	2.021	±	0.94	

Appendix 4.6 Encoding Phase LPC Component in the 400 to 800 millisecond latency window. Means, SEMs for the five-way treatment x region x valence x hemisphere x glucoregulation mixed factorial ANOVA. Significant effects and interactions are indicated (Gluc = Glucoregulation, Tr =Treatment, Reg = Region, Hem = Hemisphere, Val = Valence) (*p<0.05), **p<0.005, ***P<0.001)

Glucoregulation	Treatment	Region	Valence	Hemisphere	N	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	Glucose	Anterior	Negative	Left	11	-0.313	±	0.66	
				Midline	11	-0.383	±	0.71	
				Right	11	-0.707	±	0.69	
			Neutral	Left	11	-1.499	±	0.67	
				Midline	11	-0.788	±	0.65	
				Right	11	-0.093	±	0.55	
			Positive	Left	11	-0.794	±	0.50	
				Midline	11	0.052	±	0.58	
				Right	11	-0.561	±	0.61	
		Posterior	Negative	Left	11	0.708	±	0.50	
				Midline	11	1.181	±	0.67	
				Right	11	0.599	±	0.51	
			Neutral	Left	11	1.208	±	0.38	
				Midline	11	1.511	±	0.47	
				Right	11	1.371	±	0.56	
			Positive	Left	11	0.871	±	0.38	
				Midline	11	1.509	±	0.53	
				Right	11	0.845	±	0.53	
	Placebo	Anterior	Negative	Left	11	0.567	±	0.60	
				Midline	11	0.475	±	0.83	
				Right	11	0.769	±	0.66	
			Neutral	Left	11	-0.149	±	0.66	
				Midline	11	-0.169	±	0.61	
				Right	11	0.468	±	0.69	
			Positive	Left	11	1.305	±	0.86	
				Midline	11	0.248	±	0.60	
				Right	11	-0.094	±	0.75	
		Posterior	Negative	Left	11	0.849	±	0.66	
				Midline	11	0.86	±	0.56	
				Right	11	1.167	±	0.50	
			Neutral	Left	11	0.26	±	0.66	Gluc xTr x Reg *
				Midline	11	0.25	±	0.56	
				Right	11	0.298	±	0.64	
			Positive	Left	11	0.389	±	0.64	
				Midline	11	0.472	±	0.59	Reg x Val x Hem **
				Right	11	0.473	±	0.60	
Poorer Regulators	Glucose	Anterior	Negative	Left	7	0.16	±	0.83	
				Midline	7	0.479	±	0.89	TR x Val *
				Right	7	0.129	±	0.86	
			Neutral	Left	7	-0.583	±	0.84	
				Midline	7	-0.629	±	0.82	
				Right	7	-0.02	±	0.68	
			Positive	Left	7	-0.171	±	0.63	
				Midline	7	-0.095	±	0.73	
				Right	7	-0.565	±	0.77	
		Posterior	Negative	Left	7	0.17	±	0.63	
				Midline	7	-0.16	±	0.84	
				Right	7	0.349	±	0.64	
			Neutral	Left	7	0.76	±	0.48	
				Midline	7	0.156	±	0.59	
				Right	7	1.43	±	0.71	
			Positive	Left	7	-0.022	±	0.48	
				Midline	7	-0.816	±	0.66	
				Right	7	0.508	±	0.66	
	Placebo	Anterior	Negative	Left	7	-0.199	±	0.76	
				Midline	7	-0.114	±	1.04	
				Right	7	-0.311	±	0.82	
			Neutral	Left	7	-1.644	±	0.83	
				Midline	7	-1.599	±	0.77	
				Right	7	0.482	±	0.87	
			Positive	Left	7	-0.674	±	1.08	
				Midline	7	0.3	±	0.75	
				Right	7	0.437	±	0.94	
		Posterior	Negative	Left	7	0.886	±	0.83	
				Midline	7	0.862	±	0.70	
				Right	7	1.449	±	0.63	
			Neutral	Left	7	1.46	±	0.82	
				Midline	7	0.512	±	0.71	
				Right	7	0.975	±	0.80	
			Positive	Left	7	2.042	±	0.81	
				Midline	7	1.523	±	0.74	
				Right	7	1.642	±	0.75	

Appendix 4.7 Recognition Phase FN400 Component in the 300 to 500 millisecond latency window. Means, SEMs for the six-way treatment x word type x region x valence x hemisphere x glucoregulation mixed factorial ANOVA. Significant effects and interactions are indicated (Gluc = = Glucoregulation, Tr =Treatment, Reg = Region, Val = Valence, WdTyp = Word Type, Hem = Hemisphere. (*p<0.05), **p<0.005, ***P<0.001)

Glucoregulation	N	Treatment	Region	Valence	Word Type	Hemisphere	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	10	Glucose	Anterior	Negative	Old Word	Left	-0.131	±	0.963	
	10					Midline	-1.102	±	1.259	
	10					Right	0.029	±	0.955	
	10				New Word	Left	1.827	±	0.402	
	10					Midline	0.65	±	0.384	Reg x WdTyp x Hem *
	10					Right	1.851	±	0.353	
	10			Neutral	Old Word	Left	2.24	±	0.546	Reg x Val x WdTyp *
	10					Midline	1.005	±	0.575	
	10					Right	2.04	±	0.482	Reg x Hem **
	10				New Word	Left	1.406	±	0.411	
	10					Midline	-0.052	±	0.428	Val x WdTyp **
	10					Right	1.479	±	0.435	
	10			Positive	Old Word	Left	2.215	±	0.53	Reg x Val *
	10					Midline	0.984	±	0.601	
	10					Right	1.835	±	0.498	Val *
	10				New Word	Left	1.775	±	0.52	
	10					Midline	0.59	±	0.554	Hem ***
	10					Right	2.064	±	0.443	
	10		Posterior	Negative	Old Word	Left	1.56	±	0.743	
	10					Midline	0.689	±	0.95	
	10					Right	2.685	±	1.062	
	10				New Word	Left	1.086	±	0.766	
	10					Midline	-0.165	±	0.908	
	10					Right	1.285	±	0.772	
	10			Neutral	Old Word	Left	0.842	±	0.96	
	10					Midline	-1.011	±	0.874	
	10					Right	1.23	±	1.051	
	10				New Word	Left	0.952	±	0.735	
	10					Midline	-0.109	±	0.575	
	10					Right	1.876	±	0.773	
	10			Positive	Old Word	Left	1.282	±	1	
	10					Midline	0.343	±	0.954	
	10					Right	1.978	±	0.961	
	10				New Word	Left	1.064	±	0.927	
	10					Midline	-0.441	±	0.948	
	10					Right	0.86	±	0.966	
	10	Placebo	Anterior	Negative	Old Word	Left	-0.636	±	1.252	
	10					Midline	-0.454	±	1.557	
	10					Right	0.202	±	1.122	
	10				New Word	Left	1.701	±	0.45	
	10					Midline	0.349	±	0.476	
	10					Right	1.625	±	0.32	
	10			Neutral	Old Word	Left	1.64	±	0.583	
	10					Midline	0.231	±	0.655	
	10					Right	1.319	±	0.505	
	10				New Word	Left	1.863	±	0.409	
	10					Midline	0.211	±	0.496	
	10					Right	1.721	±	0.409	
	10			Positive	Old Word	Left	1.702	±	0.618	
	10					Midline	0.832	±	0.672	
	10					Right	2.01	±	0.538	
	10				New Word	Left	1.741	±	0.423	
	10					Midline	0.353	±	0.439	
	10					Right	1.53	±	0.383	
	10		Posterior	Negative	Old Word	Left	1.776	±	0.966	
	10					Midline	0.589	±	0.759	
	10					Right	1.967	±	1.106	
	10				New Word	Left	1.474	±	0.833	
	10					Midline	-0.311	±	0.827	
	10					Right	1.284	±	1.016	
	10			Neutral	Old Word	Left	2.103	±	0.929	
	10					Midline	-0.266	±	1.038	
	10					Right	2.382	±	1.114	
	10				New Word	Left	1.125	±	0.755	
	10					Midline	-1.039	±	0.894	
	10					Right	1.244	±	0.946	
	10			Positive	Old Word	Left	0.793	±	0.794	
	10					Midline	0.382	±	0.835	
	10					Right	2.572	±	1.385	
	10				New Word	Left	0.896	±	0.578	
	10					Midline	-0.233	±	0.803	
	10					Right	1.597	±	1.067	

Continued

Appendix 4.7 Continued

Glucoregulation	N	Treatment	Region	Valence	Word Type	Hemisphere	Mean	±	SEM
Poorer Regulators	7	Glucose	Anterior	Negative	Old Word	Left	-0.322	±	1.151
	7					Midline	-1.142	±	1.505
	7					Right	-0.023	±	1.141
	7				New Word	Left	1.915	±	0.481
	7					Midline	0.479	±	0.459
	7					Right	1.899	±	0.422
	7			Neutral	Old Word	Left	2.127	±	0.653
	7					Midline	0.27	±	0.687
	7					Right	1.288	±	0.576
	7				New Word	Left	1.688	±	0.492
	7					Midline	0.197	±	0.512
	7					Right	1.731	±	0.52
	7			Positive	Old Word	Left	2.4	±	0.633
	7					Midline	0.773	±	0.719
	7					Right	1.816	±	0.595
	7				New Word	Left	1.992	±	0.622
	7					Midline	0.607	±	0.662
	7					Right	2.125	±	0.53
	7		Posterior	Negative	Old Word	Left	-0.198	±	0.888
	7					Midline	-1.25	±	1.135
	7					Right	2.777	±	1.269
	7				New Word	Left	-0.254	±	0.915
	7					Midline	-0.736	±	1.085
	7					Right	2.48	±	0.922
	7			Neutral	Old Word	Left	0.744	±	1.147
	7					Midline	-1.184	±	1.045
	7					Right	2.81	±	1.256
	7				New Word	Left	-0.305	±	0.879
	7					Midline	-1.711	±	0.687
	7					Right	2.772	±	0.924
	7			Positive	Old Word	Left	0.051	±	1.195
	7					Midline	-1.562	±	1.14
	7					Right	2.916	±	1.148
	7				New Word	Left	0.103	±	1.108
	7					Midline	-1.265	±	1.133
	7					Right	2.298	±	1.154
	7	Placebo	Anterior	Negative	Old Word	Left	2.069	±	1.497
	7					Midline	-0.29	±	1.861
	7					Right	1.308	±	1.341
	7				New Word	Left	2.15	±	0.537
	7					Midline	0.668	±	0.568
	7					Right	1.85	±	0.383
	7			Neutral	Old Word	Left	2.774	±	0.696
	7					Midline	0.922	±	0.783
	7					Right	1.69	±	0.604
	7				New Word	Left	1.411	±	0.489
	7					Midline	-0.082	±	0.593
	7					Right	1.817	±	0.489
	7			Positive	Old Word	Left	1.772	±	0.738
	7					Midline	0.671	±	0.803
	7					Right	1.556	±	0.643
	7				New Word	Left	1.962	±	0.506
	7					Midline	0.286	±	0.525
	7					Right	1.58	±	0.458
	7		Posterior	Negative	Old Word	Left	-1.029	±	1.155
	7					Midline	-2.021	±	0.907
	7					Right	0.704	±	1.321
	7				New Word	Left	0.205	±	0.996
	7					Midline	-1.02	±	0.988
	7					Right	1.714	±	1.214
	7			Neutral	Old Word	Left	-1.716	±	1.11
	7					Midline	-2.569	±	1.24
	7					Right	0.591	±	1.331
	7				New Word	Left	-0.279	±	0.902
	7					Midline	-0.988	±	1.069
	7					Right	1.897	±	1.131
	7			Positive	Old Word	Left	-0.366	±	0.949
	7					Midline	-0.919	±	0.998
	7					Right	2.86	±	1.655
	7				New Word	Left	-0.561	±	0.691
	7					Midline	-1.455	±	0.959
	7					Right	2.223	±	1.276

Appendix 4.8 Word Recognition Phase LPC Component in the 400 to 800 millisecond latency window. Means, SEMs for the via the six-way treatment x word type x region x valence x hemisphere x glucoregulation mixed factorial ANOVA. Significant effects and interactions are indicated (Gluc = Glucoregulation, Tr =Treatment, Reg = Region, Val = Valence, WdTyp = Word Type, Hem = Hemisphere. (*p<0.05), **p<0.005, ***P<0.001)

Glucoregulation	N	Treatment	Region	Valence	Word Type	Hemisphere	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	11	Glucose	Anterior	Negative	Old Word	Left	-3.985	±	1.205	
	11					Midline	-5.072	±	1.227	
	11					Right	-2.294	±	1.185	
	11				New Word	Left	-2.15	±	0.662	
	11					Midline	-2.465	±	0.79	Val x WdTyp x Hem *
	11					Right	-1.041	±	0.737	
	11			Neutral	Old Word	Left	-3.073	±	1.566	Reg x WdTyp *
	11					Midline	-3.583	±	1.309	
	11					Right	-1.366	±	1.281	Reg *
	11				New Word	Left	-2.507	±	0.757	
	11					Midline	-3.611	±	0.884	Hem ***
	11					Right	-1.856	±	0.872	
	11			Positive	Old Word	Left	-4.242	±	1.929	
	11					Midline	-3.83	±	1.515	
	11					Right	-1.524	±	1.339	
	11				New Word	Left	-1.77	±	1.056	
	11					Midline	-2.637	±	1.208	
	11					Right	-0.813	±	1.038	
	11		Posterior	Negative	Old Word	Left	3.247	±	0.872	
	11					Midline	2.281	±	0.991	
	11					Right	3.925	±	1.152	
	11				New Word	Left	1.412	±	0.696	
	11					Midline	0.702	±	0.795	
	11					Right	1.411	±	0.638	
	11			Neutral	Old Word	Left	2.577	±	1.003	
	11					Midline	0.412	±	1.257	
	11					Right	1.793	±	1.173	
	11				New Word	Left	1.201	±	0.605	
	11					Midline	0.853	±	0.43	
	11					Right	1.787	±	0.672	
	11			Positive	Old Word	Left	3.159	±	1.167	
	11					Midline	2.018	±	1.404	
	11					Right	3.091	±	1.404	
	11				New Word	Left	1.262	±	0.798	
	11					Midline	-0.031	±	0.844	
	11					Right	0.742	±	0.822	
	11	Placebo	Anterior	Negative	Old Word	Left	-3.031	±	1.532	
	11					Midline	-4.955	±	1.654	
	11					Right	-2.908	±	1.423	
	11				New Word	Left	-1.78	±	0.888	
	11					Midline	-3.197	±	0.9	
	11					Right	-1.498	±	0.744	
	11			Neutral	Old Word	Left	-3.643	±	2.005	
	11					Midline	-5.913	±	1.59	
	11					Right	-3.335	±	1.413	
	11				New Word	Left	-1.696	±	0.802	
	11					Midline	-3.626	±	0.991	
	11					Right	-1.88	±	0.911	
	11			Positive	Old Word	Left	-3.085	±	2.442	
	11					Midline	-4.605	±	1.681	
	11					Right	-2.163	±	1.399	
	11				New Word	Left	-1.769	±	0.778	
	11					Midline	-3.118	±	0.99	
	11					Right	-1.99	±	0.909	
	11		Posterior	Negative	Old Word	Left	3.298	±	0.883	
	11					Midline	2.072	±	0.858	
	11					Right	2.602	±	1.137	
	11				New Word	Left	1.693	±	0.561	
	11					Midline	0.836	±	0.604	
	11					Right	0.529	±	0.983	
	11			Neutral	Old Word	Left	3.598	±	1.021	
	11					Midline	1.481	±	1.283	
	11					Right	2.943	±	1.356	
	11				New Word	Left	1.7	±	0.641	
	11					Midline	0.708	±	0.702	
	11					Right	1.588	±	0.822	
	11			Positive	Old Word	Left	2.345	±	0.903	
	11					Midline	1.684	±	1.069	
	11					Right	3.245	±	1.43	
	11				New Word	Left	1.423	±	0.48	
	11					Midline	0.828	±	0.572	
	11					Right	1.591	±	0.922	

Continued.

Appendix 4.8 Continued

Glucoregulation	N	Treatment	Region	Valence	Word Type	Hemisphere	Mean	±	SEM	
Poorer Regulators	7	Glucose	Anterior	Negative	Old Word	Left	-3.619	±	1.51	
	7					Midline	-4.031	±	1.538	
	7					Right	-1.899	±	1.486	
	7				New Word	Left	-1.957	±	0.83	
	7					Midline	-2.638	±	0.99	
	7					Right	-0.081	±	0.924	
	7			Neutral	Old Word	Left	-2.626	±	1.963	
	7					Midline	-4.392	±	1.641	
	7					Right	-2.676	±	1.605	
	7				New Word	Left	-2.016	±	0.949	
	7					Midline	-3.149	±	1.108	
	7					Right	-1.147	±	1.093	
	7			Positive	Old Word	Left	-2.639	±	2.419	
	7					Midline	-2.28	±	1.899	
	7					Right	-0.955	±	1.679	
	7				New Word	Left	-1.098	±	1.324	
	7					Midline	-2.737	±	1.514	
	7					Right	-0.416	±	1.302	
	7		Posterior	Negative	Old Word	Left	3.585	±	1.093	
	7					Midline	2.505	±	1.242	
	7					Right	4.438	±	1.444	
	7				New Word	Left	0.965	±	0.873	
	7					Midline	0.174	±	0.997	
	7					Right	2.499	±	0.8	
	7			Neutral	Old Word	Left	3.567	±	1.258	
	7					Midline	1.502	±	1.575	
	7					Right	4.254	±	1.47	
	7				New Word	Left	0.861	±	0.759	
	7					Midline	-0.007	±	0.54	
	7					Right	3.109	±	0.842	
	7			Positive	Old Word	Left	3.061	±	1.462	
	7					Midline	2.06	±	1.76	
	7					Right	4.402	±	1.761	
	7				New Word	Left	0.227	±	1.001	
	7					Midline	-0.401	±	1.058	
	7					Right	2.343	±	1.031	
	7	Placebo	Anterior	Negative	Old Word	Left	-1.434	±	1.921	
	7					Midline	-3.005	±	2.073	
	7					Right	-0.82	±	1.784	
	7				New Word	Left	-1.504	±	1.113	
	7					Midline	-2.705	±	1.128	
	7					Right	-1.137	±	0.933	
	7			Neutral	Old Word	Left	-1.252	±	2.514	
	7					Midline	-0.936	±	1.993	
	7					Right	-1.742	±	1.771	
	7				New Word	Left	-2.994	±	1.006	
	7					Midline	-4.069	±	1.242	
	7					Right	-1.329	±	1.142	
	7			Positive	Old Word	Left	-3.967	±	3.061	
	7					Midline	-1.884	±	2.108	
	7					Right	-2.275	±	1.754	
	7				New Word	Left	-1.722	±	0.975	
	7					Midline	-2.832	±	1.241	
	7					Right	-1.559	±	1.139	
	7		Posterior	Negative	Old Word	Left	2.294	±	1.107	
	7					Midline	1.301	±	1.076	
	7					Right	2.837	±	1.426	
	7				New Word	Left	1.468	±	0.703	
	7					Midline	-0.048	±	0.758	
	7					Right	2.071	±	1.233	
	7			Neutral	Old Word	Left	1.917	±	1.279	
	7					Midline	1.019	±	1.608	
	7					Right	2.345	±	1.7	
	7				New Word	Left	0.905	±	0.804	
	7					Midline	0.431	±	0.88	
	7					Right	2.316	±	1.03	
	7			Positive	Old Word	Left	2.608	±	1.132	
	7					Midline	2.255	±	1.341	
	7					Right	4.854	±	1.792	
	7				New Word	Left	0.544	±	0.602	
	7					Midline	-0.165	±	0.716	
	7					Right	2.274	±	1.155	

Appendix 4.9 Word Recognition Phase Subjective Judgements for The FN400 Component in the 300 to 500 millisecond latency window. Means and SEMs for the six-way treatment x recognition type x region x valence x hemisphere x glucoregulation mixed factorial ANOVA. Significant effects and interactions are indicated (Gluc=Glucoregulation, Tr =Treatment, Reg = Region, Val = Valence, RecTyp = Recognition Type, Hem = Hemisphere.(*p<0.05),

Glucoregulation	N	Treatment	Region	Valence	Recognition Type	Hemisphere	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	10	Glucose	Anterior	Negative	Recollection	Left	0.413	±	1.537	
	10					Midline	-0.678	±	1.785	
	10					Right	0.308	±	1.201	
	10				Familiarity	Left	-0.965	±	1.177	
	10					Midline	-2.455	±	1.178	
	10					Right	-1.316	±	1.000	
	10			Neutral	Recollection	Left	-0.583	±	1.336	
	10					Midline	-0.397	±	1.365	
	10					Right	0.083	±	1.067	Gluc x Tr x RecTyp x Val *
	10				Familiarity	Left	-2.39	±	1.712	
	10					Midline	-1.738	±	1.442	Hem *
	10					Right	0.776	±	1.517	
	10			Positive	Recollection	Left	-0.056	±	1.290	
	10					Midline	-0.075	±	1.288	
	10					Right	0.411	±	1.094	
	10				Familiarity	Left	-2.13	±	1.529	
	10					Midline	-2.374	±	1.582	
	10					Right	-1.216	±	1.178	
	10		Posterior	Negative	Recollection	Left	2.711	±	1.003	
	10					Midline	1.319	±	1.170	
	10					Right	2.974	±	1.040	
	10				Familiarity	Left	1.321	±	0.979	
	10					Midline	0.805	±	0.983	
	10					Right	2.524	±	1.356	
	10			Neutral	Recollection	Left	3.589	±	0.914	
	10					Midline	1.363	±	1.205	
	10					Right	1.823	±	0.928	
	10				Familiarity	Left	-0.307	±	1.930	
	10					Midline	-1.93	±	2.087	
	10					Right	0.144	±	1.489	
	10			Positive	Recollection	Left	2.184	±	0.921	
	10					Midline	1.336	±	1.100	
	10					Right	3.697	±	1.018	
	10				Familiarity	Left	2.985	±	1.667	
	10					Midline	1.846	±	2.155	
	10					Right	2.115	±	1.809	
	10	Placebo	Anterior	Negative	Recollection	Left	-0.344	±	0.985	
	10					Midline	-0.415	±	1.166	
	10					Right	-0.057	±	0.800	
	10				Familiarity	Left	-1.067	±	1.132	
	10					Midline	-1.72	±	1.183	
	10					Right	-0.218	±	1.521	
	10			Neutral	Recollection	Left	-1.152	±	1.261	
	10					Midline	-1.673	±	1.207	
	10					Right	-1.465	±	1.027	
	10				Familiarity	Left	-0.763	±	1.827	
	10					Midline	-2.04	±	1.999	
	10					Right	-0.978	±	1.646	
	10			Positive	Recollection	Left	-1.435	±	1.143	
	10					Midline	-2.128	±	1.346	
	10					Right	-0.848	±	1.067	
	10				Familiarity	Left	-1.006	±	1.376	
	10					Midline	0.892	±	1.802	
	10					Right	2.325	±	1.953	
	10		Posterior	Negative	Recollection	Left	1.986	±	0.744	
	10					Midline	1.469	±	0.842	
	10					Right	2.266	±	1.089	
	10				Familiarity	Left	3.227	±	1.902	
	10					Midline	2.681	±	1.740	
	10					Right	4.146	±	1.616	
	10			Neutral	Recollection	Left	2.544	±	0.940	
	10					Midline	1.504	±	1.257	
	10					Right	2.99	±	1.066	
	10				Familiarity	Left	2.918	±	2.415	
	10					Midline	1.674	±	2.841	
	10					Right	3.765	±	2.702	
	10			Positive	Recollection	Left	2.012	±	0.733	
	10					Midline	2.658	±	0.822	
	10					Right	4.22	±	1.156	
	10				Familiarity	Left	0.628	±	1.075	
	10					Midline	-0.574	±	1.508	
	10					Right	1.514	±	1.617	

Continued.

Appendix 4.9 Continued

Glucoregulation	N	Treatment	Region	Valence	Recognition Type	Hemisphere	Mean	±	SEM
Poorer Regulators	5	Glucose	Anterior	Negative	Recollection	Left	1.414	±	2.174
	5					Midline	-0.915	±	2.525
	5					Right	1.048	±	1.698
	5				Familiarity	Left	1.464	±	1.665
	5					Midline	2.944	±	1.666
	5					Right	2.999	±	1.414
	5			Neutral	Recollection	Left	0.628	±	1.890
	5					Midline	-0.998	±	1.931
	5					Right	-0.484	±	1.508
	5				Familiarity	Left	-1.837	±	2.421
	5					Midline	-3.242	±	2.039
	5					Right	0.017	±	2.145
	5			Positive	Recollection	Left	1.578	±	1.824
	5					Midline	0.582	±	1.821
	5					Right	0.655	±	1.548
	5				Familiarity	Left	-1.387	±	2.162
	5					Midline	-2.207	±	2.237
	5					Right	0.345	±	1.665
	5		Posterior	Negative	Recollection	Left	2.648	±	1.419
	5					Midline	-0.186	±	1.654
	5					Right	2.729	±	1.471
	5				Familiarity	Left	4.382	±	1.385
	5					Midline	3.071	±	1.390
	5					Right	3.864	±	1.918
	5			Neutral	Recollection	Left	2.389	±	1.293
	5					Midline	-0.019	±	1.705
	5					Right	2.598	±	1.312
	5				Familiarity	Left	1.214	±	2.730
	5					Midline	0.449	±	2.952
	5					Right	3.952	±	2.106
	5			Positive	Recollection	Left	3.031	±	1.302
	5					Midline	1.271	±	1.556
	5					Right	2.697	±	1.440
	5				Familiarity	Left	0.329	±	2.358
	5					Midline	-1.902	±	3.048
	5					Right	2.352	±	2.558
	5	Placebo	Anterior	Negative	Recollection	Left	1.029	±	1.393
	5					Midline	-1.377	±	1.649
	5					Right	0.611	±	1.131
	5				Familiarity	Left	1.197	±	1.601
	5					Midline	-0.02	±	1.673
	5					Right	0.8	±	2.151
	5			Neutral	Recollection	Left	1.061	±	1.783
	5					Midline	-0.834	±	1.706
	5					Right	-0.988	±	1.452
	5				Familiarity	Left	1.565	±	2.584
	5					Midline	0.524	±	2.827
	5					Right	1.942	±	2.328
	5			Positive	Recollection	Left	-0.052	±	1.616
	5					Midline	-2.011	±	1.903
	5					Right	-0.634	±	1.509
	5				Familiarity	Left	1.36	±	1.946
	5					Midline	1.611	±	2.549
	5					Right	2.636	±	2.762
	5		Posterior	Negative	Recollection	Left	1.71	±	1.053
	5					Midline	0.396	±	1.191
	5					Right	0.869	±	1.540
	5				Familiarity	Left	-0.565	±	2.690
	5					Midline	-2.72	±	2.461
	5					Right	-2.709	±	2.285
	5			Neutral	Recollection	Left	-0.366	±	1.329
	5					Midline	-0.582	±	1.778
	5					Right	1.474	±	1.508
	5				Familiarity	Left	-0.979	±	3.416
	5					Midline	-2.735	±	4.018
	5					Right	-0.667	±	3.821
	5			Positive	Recollection	Left	3.451	±	1.037
	5					Midline	0.871	±	1.163
	5					Right	3.2	±	1.635
	5				Familiarity	Left	1.079	±	1.520
	5					Midline	0.33	±	2.133
	5					Right	2.069	±	2.287

Appendix 4.10 Word Recognition Phase Subjective Judgements for The LPC Component in the 400 to 500 millisecond latency window. Means, SEMs for the six-way treatment x recognition type x region x valence x hemisphere x glucoregulation mixed factorial ANOVA. Significant effects and interactions are indicated (Gluc = Glucoregulation, Tr =Treatment, Reg = Region, Val = Valence, RecTyp = Recognition Type, Hem = Hemisphere. (*p<0.05)

Glucoregulation	N	Treatment	Region	Valence	Recognition Type	Hemisphere	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	10	Glucose	Anterior	Negative	Recollection	Left	-2.578	±	1.179	
	10					Midline	-3.322	±	1.487	
	10					Right	-1.055	±	1.040	
	10				Familiarity	Left	-2.178	±	1.127	
	10					Midline	-3.774	±	1.184	
	10					Right	-1.576	±	1.237	
	10			Neutral	Recollection	Left	-2.495	±	1.133	
	10					Midline	-2.732	±	1.288	
	10					Right	-1.3	±	1.012	Tr x Val x RecTyp *
	10				Familiarity	Left	-3.037	±	1.431	
	10					Midline	-2.858	±	1.293	Gluc x RecTyp *
	10					Right	-0.13	±	1.358	
	10			Positive	Recollection	Left	-1.796	±	1.211	Tr x RecTyp *
	10					Midline	-2.376	±	1.186	
	10					Right	-0.943	±	1.120	RecTyp *
	10				Familiarity	Left	-3.637	±	1.362	
	10					Midline	-3.25	±	1.526	Region *
	10					Right	-1.193	±	1.118	
	10		Posterior	Negative	Recollection	Left	2.586	±	0.873	Hem **
	10					Midline	1.111	±	0.967	
	10					Right	3.013	±	1.221	
	10				Familiarity	Left	1.252	±	0.913	
	10					Midline	0.722	±	1.086	
	10					Right	3.562	±	1.089	
	10			Neutral	Recollection	Left	2.633	±	0.830	
	10					Midline	-0.145	±	0.991	
	10					Right	1.526	±	0.862	
	10				Familiarity	Left	1.776	±	1.440	
	10					Midline	0.302	±	1.499	
	10					Right	1.635	±	1.086	
	10			Positive	Recollection	Left	2.023	±	0.861	
	10					Midline	0.586	±	0.872	
	10					Right	2.106	±	0.912	
	10				Familiarity	Left	2.475	±	1.096	
	10					Midline	0.997	±	1.168	
	10					Right	1.294	±	1.170	
	10	Placebo	Anterior	Negative	Recollection	Left	-2.273	±	0.959	
	10					Midline	-3.313	±	1.172	
	10					Right	-1.929	±	1.021	
	10				Familiarity	Left	-3.144	±	0.974	
	10					Midline	-4.124	±	1.198	
	10					Right	-2.052	±	1.626	
	10			Neutral	Recollection	Left	-2.992	±	1.143	
	10					Midline	-4.138	±	1.115	
	10					Right	-2.419	±	0.970	
	10				Familiarity	Left	-3.532	±	1.611	
	10					Midline	-5.707	±	1.889	
	10					Right	-3.215	±	1.790	
	10			Positive	Recollection	Left	-3.324	±	1.115	
	10					Midline	-5.105	±	1.190	
	10					Right	-2.677	±	1.145	
	10				Familiarity	Left	-2.301	±	2.049	
	10					Midline	-1.863	±	1.512	
	10					Right	0.968	±	1.558	
	10		Posterior	Negative	Recollection	Left	2.573	±	0.606	
	10					Midline	1.822	±	0.694	
	10					Right	2.38	±	1.023	
	10				Familiarity	Left	2.313	±	1.216	
	10					Midline	1.271	±	1.155	
	10					Right	2.978	±	1.276	
	10			Neutral	Recollection	Left	2.419	±	0.738	
	10					Midline	0.443	±	1.009	
	10					Right	2.234	±	0.926	
	10				Familiarity	Left	3.176	±	1.486	
	10					Midline	1.282	±	1.628	
	10					Right	3.523	±	1.578	
	10			Positive	Recollection	Left	1.703	±	0.724	
	10					Midline	1.373	±	0.867	
	10					Right	3.188	±	1.057	
	10				Familiarity	Left	0.801	±	0.751	
	10					Midline	0.263	±	0.936	
	10					Right	1.618	±	1.348	

Continued

Appendix 4.10 continued

Glucoregulation	N	Treatment	Region	Valence	Recognition Type	Hemisphere	Mean	±	SEM
Poorer Regulators	5	Glucose	Anterior	Negative	Recollection	Left	-1.597	±	1.667
	5					Midline	-3.547	±	2.102
	5					Right	-0.781	±	1.471
	5				Familiarity	Left	-4.187	±	1.594
	5					Midline	-4.955	±	1.675
	5					Right	-2.099	±	1.749
	5			Neutral	Recollection	Left	-1.707	±	1.602
	5					Midline	-3.376	±	1.822
	5					Right	-1.803	±	1.431
	5				Familiarity	Left	-2.695	±	2.024
	5					Midline	-4.716	±	1.829
	5					Right	-1.476	±	1.920
	5			Positive	Recollection	Left	-1.526	±	1.713
	5					Midline	-2.058	±	1.677
	5					Right	-1.228	±	1.584
	5				Familiarity	Left	-3.499	±	1.926
	5					Midline	-4.529	±	2.158
	5					Right	-0.991	±	1.581
	5		Posterior	Negative	Recollection	Left	4.16	±	1.235
	5					Midline	1.794	±	1.367
	5					Right	3.44	±	1.727
	5				Familiarity	Left	3.484	±	1.292
	5					Midline	2.121	±	1.535
	5					Right	4.156	±	1.540
	5			Neutral	Recollection	Left	4.414	±	1.174
	5					Midline	1.976	±	1.401
	5					Right	3.057	±	1.220
	5				Familiarity	Left	2.313	±	2.036
	5					Midline	0.804	±	2.119
	5					Right	3.66	±	1.535
	5			Positive	Recollection	Left	4.909	±	1.217
	5					Midline	3.287	±	1.233
	5					Right	4.702	±	1.290
	5				Familiarity	Left	0.894	±	1.550
	5					Midline	-0.897	±	1.652
	5					Right	2.905	±	1.654
	5	Placebo	Anterior	Negative	Recollection	Left	-2.252	±	1.356
	5					Midline	-3.552	±	1.657
	5					Right	-1.556	±	1.444
	5				Familiarity	Left	-1.849	±	1.377
	5					Midline	-2.763	±	1.694
	5					Right	-1.478	±	2.299
	5			Neutral	Recollection	Left	-1.512	±	1.616
	5					Midline	-1.945	±	1.577
	5					Right	-2.738	±	1.372
	5				Familiarity	Left	-0.829	±	2.278
	5					Midline	-1.466	±	2.672
	5					Right	0.936	±	2.531
	5			Positive	Recollection	Left	-2.458	±	1.577
	5					Midline	-4.352	±	1.682
	5					Right	-2.266	±	1.619
	5				Familiarity	Left	-0.83	±	2.898
	5					Midline	-1.013	±	2.139
	5					Right	-0.007	±	2.203
	5		Posterior	Negative	Recollection	Left	3.185	±	0.857
	5					Midline	1.965	±	0.981
	5					Right	2.501	±	1.447
	5				Familiarity	Left	2.099	±	1.720
	5					Midline	0.29	±	1.634
	5					Right	0.087	±	1.804
	5			Neutral	Recollection	Left	2.555	±	1.044
	5					Midline	1.828	±	1.427
	5					Right	3.454	±	1.310
	5				Familiarity	Left	0.263	±	2.101
	5					Midline	0.351	±	2.302
	5					Right	1.981	±	2.232
	5			Positive	Recollection	Left	4.276	±	1.024
	5					Midline	2.957	±	1.227
	5					Right	4.232	±	1.495
	5				Familiarity	Left	2.491	±	1.062
	5					Midline	2.821	±	1.324
	5					Right	3.062	±	1.906

5 Appendices

Appendix 5.1 Chapter 5 Participant Health Screen and Demographic Data.

Participant	Smoker	Number Per Day	Allergies to food or drinks	Self-report in good health	High Blood Pressure Diagnisis	Sex	Age	Ethnicity	Glasses/Lenses	Handedness	Physically Active	How many Hours PW	Familial Diabetes	Gestational Diabetes	Education Years	Height (metres)	Weight (Kgs)	BMI	Hip Measuremant	Waist Measurement	Waist/Hip Ratio
1	No	0	No	Yes	No	F	19	Caucasian	No	Right	Yes	5	No	No	15	1.61	85	32.79	117	97	0.83
2	Yes	20	No	Yes	No	F	30	Caucasian	No	Right	Yes	20	Yes	No	14	1.73	78	26.06	109	101	0.93
3	No	0	No	Yes	No	F	19	Caucasian	Yes	Right	Yes	6	No	No	15	1.8	70	21.60	99	79	0.80
4	No	0	No	Yes	No	F	18	Caucasian	No	Right	Yes	4.5	No	No	14	1.68	123	43.58	137	117	0.85
5	No	0	No	Yes	No	F	33	Caucasian	Yes	Right	Yes	5.5	No	No	15	1.69	66	23.11	98	84	0.86
6	Yes	15	No	Yes	No	F	33	Caucasian	Yes	Right	Yes	5	No	No	15	1.71	61	20.86	88	79	0.90
7	No	0	No	Yes	No	F	22	Mixed	No	Right	No	0	No	No	16	1.55	48	19.98	85	66	0.78
8	No	0	No	Yes	No	F	23	Caucasian	No	Right	Yes	6	No	No	18	1.62	110	41.91	132	118	0.89
9	No	0	No	Yes	No	M	33	Caucasian	Yes	Left	Yes	13	No	N/A	14	1.79	68	21.22	98	81	0.83
10	No	0	No	Yes	No	F	19	Caucasian	No	Right	Yes	7	No	No	14	1.61	48	18.52	79	62	0.78
12	No	0	No	Yes	No	F	19	Caucasian	No	Right	No	0	No	No	14	1.7	73	25.26	108	79	0.73
13	No	0	No	Yes	No	M	20	Caucasian	Yes	Right	Yes	3	No	N/A	16	1.79	65	20.29	89	64	0.72
14	No	0	No	Yes	No	F	20	Caucasian	Yes	Right	Yes	2	No	No	16	1.74	71	23.45	99	81	0.82
15	No	0	No	Yes	No	F	19	Caucasian	Yes	Left	Yes	1.5	No	No	15	1.66	68	24.68	98	77	0.79
16	No	0	No	Yes	No	F	25	Caucasian	No	Right	No	0	No	No	18	1.65	56	20.57	93	70	0.75
17	No	0	No	Yes	No	F	22	Caucasian	Yes	Right	Yes	5	No	No	18	1.75	90	29.39	112	85	0.76
18	No	0	No	Yes	No	F	25	Caucasian	No	Right	Yes	20	Yes	No	20	1.72	77	26.03	109	81	0.74
19	No	0	No	Yes	No	F	22	Caucasian	Yes	Right	Yes	3.5	No	No	22	1.67	64	22.95	100	77	0.77
20	Yes	0.5	No	Yes	No	M	25	Caucasian	No	Right	Yes	30	No	N/A	20	1.85	94	27.47	114	99	0.87
21	No	0	No	Yes	No	F	20	Caucasian	Yes	Right	Yes	5	No	No	16	1.73	69	23.05	99	72	0.73
22	No	0	No	Yes	No	F	20	Caucasian	No	Right	No	0	No	No	15	1.77	69	22.02	101	75	0.74
23	No	0	No	Yes	No	M	20	Black	No	Right	Yes	5	No	N/A	14	1.71	73	24.96	95	77	0.81
24	No	0	No	Yes	No	F	19	Caucasian	No	Right	No	0	No	No	15	1.69	78	27.31	102	78	0.76
25	No	0	No	Yes	No	F	18	Mixed	Yes	Right	Yes	7	No	No	14	1.66	58	21.05	92	71	0.77
26	No	0	No	Yes	No	F	21	Caucasian	No	Right	Yes	4.5	No	No	17	1.63	63	23.71	102	79	0.77
27	No	0	No	Yes	No	F	21	Caucasian	Yes	Right	No	0	No	No	15	1.67	94	33.71	116	91	0.78
28	No	0	No	Yes	No	F	19	Caucasian	Yes	Right	Yes	5	No	No	14	1.62	81.5	31.05	110	91	0.83

Appendix 5.2 Chapter 5 Participant Health Screen and Demographic Overview.

Characteristic	Type	Count	Mean	SD
Sex	Male	4		
	Female	23		
Ethnicity	Caucasian	24		
	Black	1		
	Oriental	0		
	Mixed	2		
	Other	0		
Handedness	Right	25		
	Left	2		
Glasses or Lenses	No	14		
	Yes	13		
Age			22.37	4.68
Education in Years			15.89	2.15
Height in Metres			1.70	0.07
Weight in Kgs			74.09	17.08
Waist in Cms			82.63	13.98
Hips in Cms			103.00	13.09
Body Mass Index (BMI)			25.80	6.24
Waist to Hip Ratio (WHR)			0.80	0.06

Appendix 5.3 Chapter 5 T2DM Risk Score Questions and Penalties.

Known T2DM Risks	Risk Penalty
What is your gender?	Male = 1
If you are a woman, have you ever been diagnosed with gestational diabetes?	Yes = 10
Please tell us here what your ethnicity is?	Non-Caucasian = 6
Have you ever been diagnosed with high blood pressure?	Yes = 10
Do you smoke cigarettes or use tobacco products (such as vaping) on a daily basis?	Yes = 10
Do you have a parent, sibling or child with diabetes?	Yes = 5
What is your waist measurement in centimetres?	<90=0 / 90-99.9=4 / 100-109.9=6 / >110=9
Body mass index	<25=0 / 25-29.9=3 / 30-34.9=5 / >35=8
Are you physically active?	No = 5

Appendix 5.4 Chapter 5 Health and Demographic Screen with Associated Type 2 Diabetes Risk Assessment Scores.

Participant	Smoker	Number Per Day	Smoking Risk Score	Allergies to food or drinks	Self-report in good health	High Blood Pressure	High BP Risk Score	Sex	Sex Risk Score	Age	Ethnicity	Ethnicity Risk Score	Glasses/Lenses	Handedness	Physically Active	How many Hours PW	Physicaly Active Risk Score	Familial Diabetes	Familial Diabetes Risk Score	Gestational Diabetes	Gestational Diabetes Risk Score	Education Years	Height (metres)	Weight (Kgs)	BMI	BMI Risk Score	Hip Measuremant	Waist Measurement	Waist Measurement Risk Score	Waist/Hip Ratio	TOTAL RISK SCORE
1	No	0	0	No	Yes	No	0	F	0	19	Caucasian	0	No	Right	Yes	5	0	No	0	No	0	15	1.61	85	32.79	5	117	97	4	0.83	9
2	Yes	20	10	No	Yes	No	0	F	0	30	Caucasian	0	No	Right	Yes	20	0	Yes	5	No	0	14	1.73	78	26.06	3	109	101	6	0.93	24
3	No	0	0	No	Yes	No	0	F	0	19	Caucasian	0	Yes	Right	Yes	6	0	No	0	No	0	15	1.8	70	21.60	0	99	79	0	0.80	0
4	No	0	0	No	Yes	No	0	F	0	18	Caucasian	0	No	Right	Yes	4.5	0	No	0	No	0	14	1.68	123	43.58	8	137	117	9	0.85	17
5	No	0	0	No	Yes	No	0	F	0	33	Caucasian	0	Yes	Right	Yes	5.5	0	No	0	No	0	15	1.69	66	23.11	0	98	84	0	0.86	0
6	Yes	15	10	No	Yes	No	0	F	0	33	Caucasian	0	Yes	Right	Yes	5	0	No	0	No	0	15	1.71	61	20.86	0	88	79	0	0.90	10
7	No	0	0	No	Yes	No	0	F	0	22	Mixed	6	No	Right	No	0	5	No	0	No	0	16	1.55	48	19.98	0	85	66	0	0.78	11
8	No	0	0	No	Yes	No	0	F	0	23	Caucasian	0	No	Right	Yes	6	0	No	0	No	0	18	1.62	110	41.91	8	132	118	9	0.89	17
9	No	0	0	No	Yes	No	0	M	1	33	Caucasian	0	Yes	Left	Yes	13	0	No	0		0	14	1.79	68	21.22	0	98	81	0	0.83	1
10	No	0	0	No	Yes	No	0	F	0	19	Caucasian	0	No	Right	Yes	7	0	No	0	No	0	14	1.61	48	18.52	0	79	62	0	0.78	0
12	No	0	0	No	Yes	No	0	F	0	19	Caucasian	0	No	Right	No	0	5	No	0	No	0	14	1.7	73	25.26	3	108	79	0	0.73	8
13	No	0	0	No	Yes	No	0	M	1	20	Caucasian	0	Yes	Right	Yes	3	0	No	0		0	16	1.79	65	20.29	0	89	64	0	0.72	1
14	No	0	0	No	Yes	No	0	F	0	20	Caucasian	0	Yes	Right	Yes	2	0	No	0	No	0	16	1.74	71	23.45	0	99	81	0	0.82	0
15	No	0	0	No	Yes	No	0	F	0	19	Caucasian	0	Yes	Left	Yes	1.5	0	No	0	No	0	15	1.66	68	24.68	0	98	77	0	0.79	0
16	No	0	0	No	Yes	No	0	F	0	25	Caucasian	0	No	Right	No	0	5	No	0	No	0	18	1.65	56	20.57	0	93	70	0	0.75	5
17	No	0	0	No	Yes	No	0	F	0	22	Caucasian	0	Yes	Right	Yes	5	0	No	0	No	0	18	1.75	90	29.39	3	112	85	0	0.76	3
18	No	0	0	No	Yes	No	0	F	0	25	Caucasian	0	No	Right	Yes	20	0	Yes	5	No	0	20	1.72	77	26.03	3	109	81	0	0.74	8
19	No	0	0	No	Yes	No	0	F	0	22	Caucasian	0	Yes	Right	Yes	3.5	0	No	0	No	0	22	1.67	64	22.95	0	100	77	0	0.77	0
20	Yes	1	10	No	Yes	No	0	M	1	25	Caucasian	0	No	Right	Yes	30	0	No	0		0	20	1.85	94	27.47	3	114	99	4	0.87	18
21	No	0	0	No	Yes	No	0	F	0	20	Caucasian	0	Yes	Right	Yes	5	0	No	0	No	0	16	1.73	69	23.05	0	99	72	0	0.73	0
22	No	0	0	No	Yes	No	0	F	0	20	Caucasian	0	No	Right	No	0	5	No	0	No	0	15	1.77	69	22.02	0	101	75	0	0.74	5
23	No	0	0	No	Yes	No	0	M	1	20	Black	6	No	Right	Yes	5	0	No	0		0	14	1.71	73	24.96	0	95	77	0	0.81	7
24	No	0	0	No	Yes	No	0	F	0	19	Caucasian	0	No	Right	No	0	5	No	0	No	0	15	1.69	78	27.31	3	102	78	0	0.76	8
25	No	0	0	No	Yes	No	0	F	0	18	Mixed	6	Yes	Right	Yes	7	0	No	0	No	0	14	1.66	58	21.05	0	92	71	0	0.77	6
26	No	0	0	No	Yes	No	0	F	0	21	Caucasian	0	No	Right	Yes	4.5	0	No	0	No	0	17	1.63	63	23.71	0	102	79	0	0.77	0
27	No	0	0	No	Yes	No	0	F	0	21	Caucasian	0	Yes	Right	No	0	5	No	0	No	0	15	1.67	94	33.71	8	116	91	4	0.78	17
28	No	0	0	No	Yes	No	0	F	0	19	Caucasian	0	Yes	Right	Yes	5	0	No	0	No	0	14	1.62	81.5	31.05	5	110	91	4	0.83	9

Appendix 5.5 ECG Analysis of Heart Rate Means Over 0 - 1 Second, 0 - 2 Seconds And 0 - 3 Seconds post presentation of stimuli during the encoding phase. Means, SEMs for the five-way mixed factorial treatment x demand x valence x time x glucoregulation ANOVA. Significant effects and interactions are indicated (Gluc = Glucoregulation, Tr =Treatment (*p<0.05), **p<0.005)

Glucoregulation	Treatment	Demand	Valence	Time	N	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	Glucose	Low Demand	Negative	0 - 1 sec	13	77.046	±	2.441	
				0 - 2 sec	13	77.016	±	2.415	
				0 - 3 sec	13	76.718	±	2.391	
			Neutral	0 - 1 sec	13	77.856	±	2.398	
				0 - 2 sec	13	77.363	±	2.408	
				0 - 3 sec	13	77.37	±	2.409	
			Positive	0 - 1 sec	13	77.332	±	2.413	
				0 - 2 sec	13	76.526	±	2.355	
				0 - 3 sec	13	76.66	±	2.291	
		High Demand	Negative	0 - 1 sec	13	79.036	±	2.789	
				0 - 2 sec	13	79.009	±	2.773	
				0 - 3 sec	13	79.006	±	2.789	
			Neutral	0 - 1 sec	13	77.107	±	2.416	
				0 - 2 sec	13	77.087	±	2.405	
				0 - 3 sec	13	77.006	±	2.412	
			Positive	0 - 1 sec	13	79.031	±	2.741	
				0 - 2 sec	13	79.277	±	2.757	
				0 - 3 sec	13	79.556	±	2.742	
	Placebo	Low Demand	Negative	0 - 1 sec	13	73.633	±	2.211	
				0 - 2 sec	13	73.36	±	2.185	
				0 - 3 sec	13	72.889	±	2.118	
			Neutral	0 - 1 sec	13	71.637	±	1.995	
				0 - 2 sec	13	71.707	±	2.046	
				0 - 3 sec	13	71.591	±	2.067	
			Positive	0 - 1 sec	13	74.374	±	2.297	
				0 - 2 sec	13	73.223	±	2.238	
				0 - 3 sec	13	73.226	±	2.191	
		High Demand	Negative	0 - 1 sec	13	73.223	±	2.214	
				0 - 2 sec	13	73.335	±	2.219	
				0 - 3 sec	13	73.184	±	2.2	
			Neutral	0 - 1 sec	13	72.331	±	2.116	
				0 - 2 sec	13	72.336	±	2.095	
				0 - 3 sec	13	72.181	±	2.064	
			Positive	0 - 1 sec	13	72.96	±	2.213	
				0 - 2 sec	13	73.078	±	2.246	
				0 - 3 sec	13	72.793	±	2.192	Tr * Gluc x Dem x Val *
Poorer Regulators	Glucose	Low Demand	Negative	0 - 1 sec	11	78.784	±	2.653	
				0 - 2 sec	11	78.745	±	2.625	
				0 - 3 sec	11	78.968	±	2.599	
			Neutral	0 - 1 sec	11	75.66	±	2.607	
				0 - 2 sec	11	75.657	±	2.618	
				0 - 3 sec	11	75.761	±	2.619	
			Positive	0 - 1 sec	11	78.857	±	2.623	
				0 - 2 sec	11	78.886	±	2.56	
				0 - 3 sec	11	78.954	±	2.49	
		High Demand	Negative	0 - 1 sec	11	78.234	±	3.032	
				0 - 2 sec	11	78.317	±	3.015	
				0 - 3 sec	11	78.513	±	3.032	
			Neutral	0 - 1 sec	11	79.233	±	2.627	
				0 - 2 sec	11	79.186	±	2.614	
				0 - 3 sec	11	79.121	±	2.622	
			Positive	0 - 1 sec	11	79.339	±	2.98	
				0 - 2 sec	11	79.25	±	2.997	
				0 - 3 sec	11	79.194	±	2.981	
	Placebo	Low Demand	Negative	0 - 1 sec	11	74.851	±	2.403	
				0 - 2 sec	11	74.602	±	2.375	
				0 - 3 sec	11	74.616	±	2.302	
			Neutral	0 - 1 sec	11	74.629	±	2.168	
				0 - 2 sec	11	74.637	±	2.224	
				0 - 3 sec	11	74.85	±	2.247	
			Positive	0 - 1 sec	11	74.932	±	2.497	
				0 - 2 sec	11	74.733	±	2.433	
				0 - 3 sec	11	74.606	±	2.382	
		High Demand	Negative	0 - 1 sec	11	77.15	±	2.407	
				0 - 2 sec	11	77.263	±	2.413	
				0 - 3 sec	11	77.316	±	2.392	
			Neutral	0 - 1 sec	11	77.632	±	2.3	
				0 - 2 sec	11	77.408	±	2.277	
				0 - 3 sec	11	77.367	±	2.244	
			Positive	0 - 1 sec	11	77.068	±	2.406	
				0 - 2 sec	11	77.143	±	2.442	
				0 - 3 sec	11	77.012	±	2.383	

Appendix 5.6 Behavioural Word Recognition Old/New Accuracy Analysis. Means, SEMs for the outcomes the five-way mixed factorial treatment x demand x word type x valence x glucoregulation ANOVA. Significant effects and interactions are indicated (Gluc = Glucoregulation, Tr =Treatment, Dem = Demand, WdTyp = Word Type, Val = Valence) (*p<0.05), **p<0.005, ***P<0.001)

Outcome	Gluco-regulation	Treatment	Demand	Word Type	N	Valence	Mean	±	SEM	Significant Effects and Interactions
% Accurate	Better Regulators	Glucose	Low Demand Encoding	Old Word	12	Negative	76.67	±	6.05	
					12	Neutral	81.11	±	4.00	
					12	Positive	78.89	±	5.91	
				New Word	12	Negative	92.22	±	3.46	
					12	Neutral	95.28	±	2.79	
					12	Positive	90.00	±	3.55	
			High Demand Encoding	Old Word	12	Negative	66.67	±	6.50	
					12	Neutral	69.17	±	5.66	
					12	Positive	66.11	±	7.46	
				New Word	12	Negative	91.11	±	4.11	
					12	Neutral	94.44	±	3.39	
					12	Positive	84.44	±	4.63	
		Placebo	Low Demand Encoding	Old Word	12	Negative	76.67	±	5.99	
					12	Neutral	79.17	±	4.32	
					12	Positive	78.89	±	5.76	
				New Word	12	Negative	96.67	±	2.17	
					12	Neutral	94.17	±	2.62	
					12	Positive	91.67	±	4.14	
			High Demand Encoding	Old Word	12	Negative	70.00	±	6.07	Dem x WdTyp *
					12	Neutral	65.83	±	5.28	
					12	Positive	65.00	±	6.17	
				New Word	12	Negative	91.11	±	3.38	Gluc*
					12	Neutral	89.72	±	3.34	
					12	Positive	87.22	±	4.29	
	Poorer Regulators	Glucose	Low Demand Encoding	Old Word	14	Negative	66.67	±	5.60	Dem *
					14	Neutral	66.43	±	3.70	
					14	Positive	65.24	±	5.47	
				New Word	14	Negative	86.67	±	3.21	WdTyp ***
					14	Neutral	89.05	±	2.58	
					14	Positive	84.76	±	3.29	
			High Demand Encoding	Old Word	14	Negative	60.95	±	6.02	
					14	Neutral	61.19	±	5.24	Valence **
					14	Positive	54.29	±	6.91	
				New Word	14	Negative	81.91	±	3.81	
					14	Neutral	85.71	±	3.14	
					14	Positive	85.24	±	4.29	
		Placebo	Low Demand Encoding	Old Word	14	Negative	70.95	±	5.54	
					14	Neutral	74.05	±	4.00	
					14	Positive	64.29	±	5.33	
				New Word	14	Negative	90.00	±	2.01	
					14	Neutral	91.91	±	2.42	
					14	Positive	81.91	±	3.83	
			High Demand Encoding	Old Word	14	Negative	63.81	±	5.62	
					14	Neutral	56.91	±	4.88	
					14	Positive	58.57	±	5.71	
				New Word	14	Negative	82.86	±	3.13	
					14	Neutral	89.29	±	3.09	
					14	Positive	81.43	±	3.97	

Appendix 5.7 Encoding Phase P1 Component in the 60 to 130 millisecond latency window. Means, SEMs for the ERP analysis of the 6-way repeated-measures treatment x demand x region x valence x hemisphere x glucoregulation ANOVA. Significant effects and interactions are indicated (Gluc = Glucoregulation, Tr =Treatment ,Dem Demand, Reg = Region, Hem = Hemisphere, Val = Valence) (*p<0.05), **p<0.005, ***P<0.001)

Outcome	Gluco-regulation	Treatment	Demand	Region	Valence	Hemisphere	N	Mean	±	SEM	Significant Effects and Interactions
P100 Component Mean Amplitudes in Millivolts	Better Regulators	Glucose	Low Demand Encoding	Anterior	Negative	Left	12	-0.123	±	0.54	
						Midline	12	-0.255	±	0.55	
						Right	12	-0.421	±	0.57	
					Neutral	Left	12	-0.189	±	0.44	
						Midline	12	-0.14	±	0.39	
						Right	12	0.005	±	0.36	
					Positive	Left	12	-1.333	±	0.50	
						Midline	12	-0.998	±	0.39	
						Right	12	-0.263	±	0.44	
				Posterior	Negative	Left	12	0.674	±	0.53	
						Midline	12	-0.499	±	0.63	
						Right	12	-0.081	±	0.78	
					Neutral	Left	12	0.164	±	0.39	
						Midline	12	-0.458	±	0.37	
						Right	12	0.22	±	0.57	
					Positive	Left	12	0.314	±	0.49	
						Midline	12	-0.113	±	0.52	
						Right	12	0.464	±	0.59	
			High Demand Encoding	Anterior	Negative	Left	12	-0.541	±	0.41	
						Midline	12	-0.51	±	0.39	
						Right	12	-0.432	±	0.43	
					Neutral	Left	12	-0.541	±	0.41	
						Midline	12	-0.51	±	0.39	
						Right	12	-0.432	±	0.43	
					Positive	Left	12	-0.853	±	0.65	
						Midline	12	-0.626	±	0.51	
						Right	12	-0.549	±	0.32	
				Posterior	Negative	Left	12	0.58	±	0.37	
						Midline	12	-0.367	±	0.40	
						Right	12	0.72	±	0.53	
					Neutral	Left	12	0.58	±	0.37	Tr x Reg x Val x Hem*
						Midline	12	-0.367	±	0.40	
						Right	12	0.72	±	0.53	
					Positive	Left	12	0.454	±	0.36	Gluc x Reg x Hem *
						Midline	12	0.316	±	0.35	
						Right	12	0.604	±	0.48	Dem x Val x Hem*
		Placebo	Low Demand Encoding	Anterior	Negative	Left	12	-0.885	±	0.47	
						Midline	12	-0.624	±	0.46	Reg x Hem**
						Right	12	-0.465	±	0.45	
					Neutral	Left	12	-0.503	±	0.40	Reg *
						Midline	12	-0.394	±	0.39	
						Right	12	-0.627	±	0.36	Hem***
					Positive	Left	12	-0.206	±	0.53	
						Midline	12	-0.264	±	0.50	
						Right	12	0.229	±	0.61	
				Posterior	Negative	Left	12	0.602	±	0.37	
						Midline	12	-0.32	±	0.60	
						Right	12	0.654	±	0.68	
					Neutral	Left	12	0.583	±	0.48	
						Midline	12	-0.054	±	0.51	
						Right	12	0.223	±	0.54	
					Positive	Left	12	0.281	±	0.47	
						Midline	12	-0.966	±	0.59	
						Right	12	0.369	±	0.60	
			High Demand Encoding	Anterior	Negative	Left	12	-0.333	±	0.40	
						Midline	12	-0.129	±	0.38	
						Right	12	0.308	±	0.46	
					Neutral	Left	12	-0.333	±	0.40	
						Midline	12	-0.129	±	0.38	
						Right	12	0.308	±	0.46	
					Positive	Left	12	-0.968	±	0.45	
						Midline	12	-0.81	±	0.36	
						Right	12	-0.437	±	0.41	
				Posterior	Negative	Left	12	0.591	±	0.44	
						Midline	12	-0.197	±	0.45	
						Right	12	0.413	±	0.46	
					Neutral	Left	12	0.591	±	0.44	
						Midline	12	-0.197	±	0.45	
						Right	12	0.413	±	0.46	
					Positive	Left	12	1.062	±	0.46	
						Midline	12	0.26	±	0.53	
						Right	12	0.788	±	0.47	
					Negative	Left	12	-0.832	±	0.54	
						Midline	12	-0.699	±	0.55	
						Right	12	-0.212	±	0.57	

Continued.

Appendix 5.7 Continued

P100 Component Mean Amplitudes in Millivolts						Right	12	0.415	±	0.46
					Positive	Left	12	1.062	±	0.46
						Midline	12	0.26	±	0.53
						Right	12	0.788	±	0.47
	Poorer Regulators	Glucose	Low Demand Encoding	Anterior	Negative	Left	12	-0.832	±	0.54
						Midline	12	-0.699	±	0.55
						Right	12	-0.212	±	0.57
					Neutral	Left	12	-0.215	±	0.44
						Midline	12	-0.602	±	0.39
						Right	12	-0.637	±	0.36
					Positive	Left	12	-0.778	±	0.50
						Midline	12	-0.84	±	0.39
						Right	12	-0.554	±	0.44
				Posterior	Negative	Left	12	0.648	±	0.53
						Midline	12	0.156	±	0.63
						Right	12	1.483	±	0.78
					Neutral	Left	12	0.33	±	0.39
						Midline	12	-0.082	±	0.37
						Right	12	1.226	±	0.57
					Positive	Left	12	0.513	±	0.49
						Midline	12	0.223	±	0.52
						Right	12	1.481	±	0.59
			High Demand Encoding	Anterior	Negative	Left	12	-0.143	±	0.41
						Midline	12	-0.42	±	0.39
						Right	12	-0.41	±	0.43
					Neutral	Left	12	-0.143	±	0.41
						Midline	12	-0.42	±	0.39
						Right	12	-0.41	±	0.43
					Positive	Left	12	-0.808	±	0.65
						Midline	12	-0.612	±	0.51
						Right	12	-0.375	±	0.32
				Posterior	Negative	Left	12	-0.05	±	0.37
						Midline	12	-0.432	±	0.40
						Right	12	1.105	±	0.53
					Neutral	Left	12	-0.05	±	0.37
						Midline	12	-0.432	±	0.40
						Right	12	1.105	±	0.53
					Positive	Left	12	0.395	±	0.36
						Midline	12	0.266	±	0.35
						Right	12	0.616	±	0.48
		Placebo	Low Demand Encoding	Anterior	Negative	Left	12	-0.327	±	0.47
						Midline	12	-0.064	±	0.46
						Right	12	0.159	±	0.45
					Neutral	Left	12	-0.545	±	0.40
						Midline	12	-0.455	±	0.39
						Right	12	-0.268	±	0.36
					Positive	Left	12	-0.988	±	0.53
						Midline	12	-0.222	±	0.50
						Right	12	-0.27	±	0.61
				Posterior	Negative	Left	12	0.183	±	0.37
						Midline	12	0.119	±	0.60
						Right	12	1.198	±	0.68
					Neutral	Left	12	0.896	±	0.48
						Midline	12	0.772	±	0.51
						Right	12	1.615	±	0.54
					Positive	Left	12	0.175	±	0.47
						Midline	12	0.63	±	0.59
						Right	12	1.927	±	0.60
			High Demand Encoding	Anterior	Negative	Left	12	-0.767	±	0.40
						Midline	12	-0.526	±	0.38
						Right	12	0.012	±	0.46
					Neutral	Left	12	-0.767	±	0.40
						Midline	12	-0.526	±	0.38
						Right	12	0.012	±	0.46
					Positive	Left	12	-0.336	±	0.45
						Midline	12	0.007	±	0.36
						Right	12	-0.123	±	0.41
				Posterior	Negative	Left	12	0.069	±	0.44
						Midline	12	-0.412	±	0.45
						Right	12	1.222	±	0.46
					Neutral	Left	12	0.069	±	0.44
						Midline	12	-0.412	±	0.45
						Right	12	1.222	±	0.46
					Positive	Left	12	0.232	±	0.46
						Midline	12	0.102	±	0.53
						Right	12	0.989	±	0.47

Appendix 5.8 Encoding Phase N100 Component in the 130 to 220 millisecond latency window. Means, SEMs for the 6-way repeated-measures treatment x demand x region x valence x hemisphere x glucoregulation ANOVA. Significant effects and interactions are indicated (Gluc = Glucoregulation, Tr =Treatment, Dem = Demand, Reg = Region, Hem = Hemisphere, Val = Valence; (*p<0.05), **p<0.005, ***P<0.001)

Outcome	Gluco-regulation	Treatment	Demand	Region	Valence	Hemisphere	N	Mean	±	SEM	Significant Effects and Interactions
N100 Component Mean Amplitudes in Millivolts	Better Regulators	Glucose	Low Demand Encoding	Anterior	Negative	Left	12	1.577	±	0.50	
						Midline	12	1.378	±	0.51	
						Right	12	0.368	±	0.51	
					Neutral	Left	12	0.575	±	0.42	
						Midline	12	0.73	±	0.41	
						Right	12	0.345	±	0.38	
					Positive	Left	12	0.156	±	0.51	
						Midline	12	0.71	±	0.39	
						Right	12	0.598	±	0.40	
				Posterior	Negative	Left	12	0.674	±	0.53	
						Midline	12	-0.499	±	0.63	
						Right	12	-0.081	±	0.78	
					Neutral	Left	12	0.164	±	0.39	
						Midline	12	-0.458	±	0.37	
						Right	12	0.22	±	0.57	
					Positive	Left	12	0.314	±	0.49	
						Midline	12	-0.113	±	0.52	
						Right	12	0.464	±	0.59	
			High Demand Encoding	Anterior	Negative	Left	12	0.674	±	0.31	
						Midline	12	0.74	±	0.35	
						Right	12	0.003	±	0.44	
					Neutral	Left	12	0.674	±	0.31	
						Midline	12	0.74	±	0.35	
						Right	12	0.003	±	0.44	
					Positive	Left	12	-0.157	±	0.80	
						Midline	12	0.043	±	0.56	
						Right	12	0.38	±	0.30	
				Posterior	Negative	Left	12	0.58	±	0.37	
						Midline	12	-0.367	±	0.40	
						Right	12	0.72	±	0.53	
					Neutral	Left	12	0.58	±	0.37	
						Midline	12	-0.367	±	0.40	
						Right	12	0.72	±	0.53	
					Positive	Left	12	0.454	±	0.36	Gluc x Dem x Val x Hem*
						Midline	12	0.316	±	0.35	
						Right	12	0.604	±	0.48	Dem x Reg x Val x Hem *
		Placebo	Low Demand Encoding	Anterior	Negative	Left	12	0.899	±	0.42	
						Midline	12	1.32	±	0.45	Tr x Reg x Val x Hem **
						Right	12	0.926	±	0.41	
					Neutral	Left	12	0.724	±	0.38	Gluc x Hem*
						Midline	12	1.021	±	0.40	
						Right	12	0.602	±	0.41	Tr*
					Positive	Left	12	1.62	±	0.69	
						Midline	12	1.517	±	0.64	
						Right	12	0.964	±	0.65	
				Posterior	Negative	Left	12	0.602	±	0.37	
						Midline	12	-0.32	±	0.60	
						Right	12	0.654	±	0.68	
					Neutral	Left	12	0.583	±	0.48	
						Midline	12	-0.054	±	0.51	
						Right	12	0.223	±	0.54	
					Positive	Left	12	0.281	±	0.47	
						Midline	12	-0.966	±	0.59	
						Right	12	0.369	±	0.60	
			High Demand Encoding	Anterior	Negative	Left	12	1.126	±	0.34	
						Midline	12	1.514	±	0.34	
						Right	12	0.765	±	0.35	
					Neutral	Left	12	1.126	±	0.34	
						Midline	12	1.514	±	0.34	
						Right	12	0.765	±	0.35	
					Positive	Left	12	0.225	±	0.46	
						Midline	12	1.067	±	0.45	
						Right	12	0.837	±	0.45	
				Posterior	Negative	Left	12	0.591	±	0.44	
						Midline	12	-0.197	±	0.45	
						Right	12	0.413	±	0.46	
					Neutral	Left	12	0.591	±	0.44	
						Midline	12	-0.197	±	0.45	
						Right	12	0.413	±	0.46	
					Positive	Left	12	1.062	±	0.46	
						Midline	12	0.26	±	0.53	
						Right	12	0.788	±	0.47	
				Anterior	Negative	Left	12	0.44	±	0.50	
						Midline	12	0.796	±	0.51	
						Right	12	0.587	±	0.51	
					Neutral	Left	12	0.73	±	0.42	
						Midline	12	0.948	±	0.41	

Continued

Appendix 5.8 Continued

N100 Component Mean Amplitudes in Millivolts					Positive	Left	12	1.062	±	0.46
						Midline	12	0.26	±	0.53
						Right	12	0.788	±	0.47
	Poorer Regulators	Glucose	Low Demand Encoding	Anterior	Negative	Left	12	0.44	±	0.50
						Midline	12	0.796	±	0.51
						Right	12	0.587	±	0.51
					Neutral	Left	12	0.73	±	0.42
						Midline	12	0.948	±	0.41
						Right	12	0.261	±	0.38
					Positive	Left	12	1.159	±	0.51
						Midline	12	1.728	±	0.39
						Right	12	1.209	±	0.40
				Posterior	Negative	Left	12	0.648	±	0.53
						Midline	12	0.156	±	0.63
						Right	12	1.483	±	0.78
					Neutral	Left	12	0.33	±	0.39
						Midline	12	-0.082	±	0.37
						Right	12	1.226	±	0.57
					Positive	Left	12	0.513	±	0.49
						Midline	12	0.223	±	0.52
						Right	12	1.481	±	0.59
			High Demand Encoding	Anterior	Negative	Left	12	1.288	±	0.31
						Midline	12	1.576	±	0.35
						Right	12	0.431	±	0.44
					Neutral	Left	12	1.288	±	0.31
						Midline	12	1.576	±	0.35
						Right	12	0.431	±	0.44
					Positive	Left	12	0.233	±	0.80
						Midline	12	0.795	±	0.56
						Right	12	0.052	±	0.30
				Posterior	Negative	Left	12	-0.05	±	0.37
						Midline	12	-0.432	±	0.40
						Right	12	1.105	±	0.53
					Neutral	Left	12	-0.05	±	0.37
						Midline	12	-0.432	±	0.40
						Right	12	1.105	±	0.53
					Positive	Left	12	0.395	±	0.36
						Midline	12	0.266	±	0.35
						Right	12	0.616	±	0.48
		Placebo	Low Demand Encoding	Anterior	Negative	Left	12	0.934	±	0.42
						Midline	12	1.61	±	0.45
						Right	12	1.074	±	0.41
					Neutral	Left	12	1.145	±	0.38
						Midline	12	1.709	±	0.40
						Right	12	0.873	±	0.41
					Positive	Left	12	0.094	±	0.69
						Midline	12	1.194	±	0.64
						Right	12	0.646	±	0.65
				Posterior	Negative	Left	12	0.183	±	0.37
						Midline	12	0.119	±	0.60
						Right	12	1.198	±	0.68
					Neutral	Left	12	0.896	±	0.48
						Midline	12	0.772	±	0.51
						Right	12	1.615	±	0.54
					Positive	Left	12	0.175	±	0.47
						Midline	12	0.63	±	0.59
						Right	12	1.927	±	0.60
			High Demand Encoding	Anterior	Negative	Left	12	0.63	±	0.34
						Midline	12	1.759	±	0.34
						Right	12	1.549	±	0.35
					Neutral	Left	12	0.63	±	0.34
						Midline	12	1.759	±	0.34
						Right	12	1.549	±	0.35
					Positive	Left	12	0.852	±	0.46
						Midline	12	1.27	±	0.45
						Right	12	0.425	±	0.45
				Posterior	Negative	Left	12	0.069	±	0.44
						Midline	12	-0.412	±	0.45
						Right	12	1.222	±	0.46
					Neutral	Left	12	0.069	±	0.44
						Midline	12	-0.412	±	0.45
						Right	12	1.222	±	0.46
					Positive	Left	12	0.232	±	0.46
						Midline	12	0.102	±	0.53
						Right	12	0.989	±	0.47

Appendix 5.9 Encoding Phase P300 Component in the 210 to 330 millisecond latency window. Means, SEMs for the ERP analysis of the 6-way repeated-measures treatment x demand x region x valence x hemisphere x glucoregulation ANOVA. Significant effects and interactions are indicated (Gluc = Glucoregulation, Tr =Treatment, Dem = Demand, Reg = Region, Hem = Hemisphere, Val = Valence; (*p<0.05), **p<0.005, ***P<0.001)

Outcome	Gluco-regulation	Treatment	Demand	Region	Valence	Hemisphere	N	Mean	±	SEM	Significant Effects and Interactions
P300 Component Mean Amplitudes in Millivolts	Better Regulators	Glucose	Low Demand Encoding	Anterior	Negative	Left	21	0.435	±	0.52	
						Midline	21	0.075	±	0.51	
						Right	21	0.085	±	0.44	
					Neutral	Left	21	-0.13	±	0.39	
						Midline	21	-0.65	±	0.37	
						Right	21	-0.457	±	0.39	
					Positive	Left	21	-0.821	±	0.42	
						Midline	21	-1.186	±	0.31	
						Right	21	-0.965	±	0.34	
				Posterior	Negative	Left	21	0.506	±	0.43	
						Midline	21	-0.333	±	0.46	
						Right	21	1.374	±	0.60	
					Neutral	Left	21	0.791	±	0.44	
						Midline	21	-0.38	±	0.41	
						Right	21	1.395	±	0.37	
					Positive	Left	21	0.622	±	0.45	
						Midline	21	-0.038	±	0.52	
						Right	21	1.875	±	0.40	
			High Demand Encoding	Anterior	Negative	Left	21	0.393	±	0.18	
						Midline	21	0.75	±	0.30	
						Right	21	0.4	±	0.48	
					Neutral	Left	21	0.393	±	0.18	
						Midline	21	0.75	±	0.30	
						Right	21	0.4	±	0.48	
					Positive	Left	21	-0.777	±	0.77	
						Midline	21	-0.459	±	0.51	
						Right	21	0.05	±	0.38	
				Posterior	Negative	Left	21	0.016	±	0.30	
						Midline	21	-0.081	±	0.42	
						Right	21	0.882	±	0.30	
					Neutral	Left	21	0.016	±	0.30	
						Midline	21	-0.081	±	0.42	
						Right	21	0.882	±	0.30	Dem x Reg x Val x Hem*
					Positive	Left	21	0.043	±	0.27	
						Midline	21	-0.259	±	0.56	
						Right	21	0.747	±	0.50	Tr x Hem x Gluc *
		Placebo	Low Demand Encoding	Anterior	Negative	Left	21	-0.206	±	0.33	
						Midline	21	-0.625	±	0.46	Dem x Reg x Val*
						Right	21	-0.554	±	0.47	
					Neutral	Left	21	-0.754	±	0.42	Tr x Reg*
						Midline	21	-1.116	±	0.31	
						Right	21	-0.795	±	0.34	Dem x Val*
					Positive	Left	21	-0.223	±	0.59	
						Midline	21	-0.95	±	0.45	Dem x Reg*
						Right	21	-0.546	±	0.50	
				Posterior	Negative	Left	21	0.958	±	0.43	Dem x Hem***
						Midline	21	0.147	±	0.57	
						Right	21	1.506	±	0.55	Reg x Hem***
					Neutral	Left	21	1.464	±	0.45	
						Midline	21	0.175	±	0.50	Tr*
						Right	21	2.029	±	0.55	
					Positive	Left	21	0.647	±	0.53	Reg***
						Midline	21	-0.624	±	0.69	
						Right	21	1.676	±	0.62	Val**
			High Demand Encoding	Anterior	Negative	Left	21	0.193	±	0.31	
						Midline	21	0.394	±	0.34	Hem**
						Right	21	7.98E-05	±	0.32	
					Neutral	Left	21	0.193	±	0.31	
						Midline	21	0.394	±	0.34	
						Right	21	7.98E-05	±	0.32	
					Positive	Left	21	-0.941	±	0.59	
						Midline	21	-0.655	±	0.45	
						Right	21	-0.719	±	0.40	
				Posterior	Negative	Left	21	0.663	±	0.31	
						Midline	21	0.887	±	0.48	
						Right	21	1.744	±	0.43	
					Neutral	Left	21	0.663	±	0.31	
						Midline	21	0.887	±	0.48	
						Right	21	1.744	±	0.43	
					Positive	Left	21	0.995	±	0.39	
						Midline	21	0.618	±	0.57	
						Right	21	1.775	±	0.48	
					Negative	Left	21	-0.626	±	0.52	
						Midline	21	-0.704	±	0.51	
						Right	21	-0.7	±	0.44	

Continued

Appendix 5.9 Continued

P300 Component Mean Amplitudes in Millivolts						Right	21	1.744	±	0.45
					Positive	Left	21	0.995	±	0.39
						Midline	21	0.618	±	0.57
						Right	21	1.775	±	0.48
	Poorer Regulators	Glucose	Low Demand Encoding	Anterior	Negative	Left	21	-0.626	±	0.52
						Midline	21	-0.704	±	0.51
						Right	21	-0.7	±	0.44
					Neutral	Left	21	-1.15	±	0.39
						Midline	21	-1.132	±	0.37
						Right	21	-1.246	±	0.39
					Positive	Left	21	-0.919	±	0.42
						Midline	21	-1.206	±	0.31
						Right	21	-1.055	±	0.34
				Posterior	Negative	Left	21	1.501	±	0.43
						Midline	21	0.821	±	0.46
						Right	21	1.613	±	0.60
					Neutral	Left	21	1.619	±	0.44
						Midline	21	0.794	±	0.41
						Right	21	2.272	±	0.37
					Positive	Left	21	1.331	±	0.45
						Midline	21	0.517	±	0.52
						Right	21	1.571	±	0.40
			High Demand Encoding	Anterior	Negative	Left	21	0.238	±	0.18
						Midline	21	0.523	±	0.30
						Right	21	-0.12	±	0.48
					Neutral	Left	21	0.238	±	0.18
						Midline	21	0.523	±	0.30
						Right	21	-0.12	±	0.48
					Positive	Left	21	-0.935	±	0.77
						Midline	21	-0.529	±	0.51
						Right	21	-0.136	±	0.38
				Posterior	Negative	Left	21	0.224	±	0.30
						Midline	21	0.246	±	0.42
						Right	21	0.911	±	0.30
					Neutral	Left	21	0.224	±	0.30
						Midline	21	0.246	±	0.42
						Right	21	0.911	±	0.30
					Positive	Left	21	0.592	±	0.27
						Midline	21	-0.589	±	0.56
						Right	21	0.398	±	0.50
		Placebo	Low Demand Encoding	Anterior	Negative	Left	21	-0.464	±	0.33
						Midline	21	-0.494	±	0.46
						Right	21	-0.485	±	0.47
					Neutral	Left	21	-1.348	±	0.42
						Midline	21	-1.228	±	0.31
						Right	21	-1.231	±	0.34
					Positive	Left	21	-1.267	±	0.59
						Midline	21	-0.747	±	0.45
						Right	21	-0.685	±	0.50
				Posterior	Negative	Left	21	0.961	±	0.43
						Midline	21	0.808	±	0.57
						Right	21	1.511	±	0.55
					Neutral	Left	21	1.862	±	0.45
						Midline	21	0.948	±	0.50
						Right	21	2.55	±	0.55
					Positive	Left	21	1.046	±	0.53
						Midline	21	0.712	±	0.69
						Right	21	2.4	±	0.62
			High Demand Encoding	Anterior	Negative	Left	21	-0.389	±	0.31
						Midline	21	0.348	±	0.34
						Right	21	0.131	±	0.32
					Neutral	Left	21	-0.389	±	0.31
						Midline	21	0.348	±	0.34
						Right	21	0.131	±	0.32
					Positive	Left	21	-0.429	±	0.59
						Midline	21	-0.166	±	0.45
						Right	21	-1.021	±	0.40
				Posterior	Negative	Left	21	0.335	±	0.31
						Midline	21	0.781	±	0.48
						Right	21	1.777	±	0.43
					Neutral	Left	21	0.335	±	0.31
						Midline	21	0.781	±	0.48
						Right	21	1.777	±	0.43
					Positive	Left	21	1.001	±	0.39
						Midline	21	1.092	±	0.57
						Right	21	1.954	±	0.48

Appendix 5.10 Encoding Phase LPC Component in the 540 to 780 millisecond latency window. Means, SEMs for the 6-way repeated-measures treatment x demand x region x valence x hemisphere x glucoregulation ANOVA. Significant effects and interactions are indicated (Gluc = Glucoregulation, Tr =Treatment, Dem = Demand, Reg = Region, Hem = Hemisphere, Val = Valence; (*p<0.05), **p<0.005, ***P<0.001)

Outcome	Gluco-regulation	Treatment	Demand	Region	Valence	Hemisphere	N	Mean	±	SEM	Significant Effects and Interactions
LPC Component Mean Amplitudes in Millivolts	Better Regulators	Glucose	Low Demand Encoding	Anterior	Negative	Left	21	0.29	±	0.40	
						Midline	21	0.163	±	0.33	
						Right	21	-0.378	±	0.39	
					Neutral	Left	21	0.085	±	0.31	
						Midline	21	0.276	±	0.20	
						Right	21	0.079	±	0.20	
					Positive	Left	21	-0.54	±	0.42	
						Midline	21	-0.163	±	0.32	
						Right	21	-0.309	±	0.36	
				Posterior	Negative	Left	21	0.315	±	0.37	
						Midline	21	0.447	±	0.37	
						Right	21	-0.096	±	0.46	
					Neutral	Left	21	0.164	±	0.21	
						Midline	21	0.462	±	0.21	
						Right	21	0.128	±	0.24	
					Positive	Left	21	0.129	±	0.41	
						Midline	21	0.767	±	0.52	
						Right	21	0.451	±	0.43	
			High Demand Encoding	Anterior	Negative	Left	21	-0.305	±	0.22	
						Midline	21	0.036	±	0.24	
						Right	21	0.059	±	0.31	
					Neutral	Left	21	-0.305	±	0.22	
						Midline	21	0.036	±	0.24	
						Right	21	0.059	±	0.31	
					Positive	Left	21	-0.502	±	0.57	
						Midline	21	-0.096	±	0.34	
						Right	21	0.093	±	0.20	
				Posterior	Negative	Left	21	0.148	±	0.19	
						Midline	21	0.314	±	0.22	
						Right	21	0.132	±	0.24	
					Neutral	Left	21	0.148	±	0.19	
						Midline	21	0.314	±	0.22	
						Right	21	0.132	±	0.24	Gluc x Tr x Dem x Hem*
					Positive	Left	21	-0.072	±	0.20	
						Midline	21	0.152	±	0.25	
						Right	21	0.081	±	0.24	Tr x Dem x Hem**
		Placebo	Low Demand Encoding	Anterior	Negative	Left	21	-0.057	±	0.36	
						Midline	21	0.196	±	0.30	Dem x Hem***
						Right	21	0.052	±	0.38	
					Neutral	Left	21	0.222	±	0.29	Tr*
						Midline	21	0.335	±	0.24	
						Right	21	0.05	±	0.25	Hem***
					Positive	Left	21	0.187	±	0.45	
						Midline	21	0.418	±	0.39	
						Right	21	0.363	±	0.43	
				Posterior	Negative	Left	21	-0.029	±	0.34	
						Midline	21	0.466	±	0.44	
						Right	21	0.029	±	0.41	
					Neutral	Left	21	0.079	±	0.27	
						Midline	21	0.35	±	0.33	
						Right	21	-0.241	±	0.27	
					Positive	Left	21	-0.159	±	0.30	
						Midline	21	0.316	±	0.42	
						Right	21	0.063	±	0.42	
			High Demand Encoding	Anterior	Negative	Left	21	0.221	±	0.24	
						Midline	21	0.581	±	0.23	
						Right	21	4.53E-01	±	0.21	
					Neutral	Left	21	0.221	±	0.24	
						Midline	21	0.581	±	0.23	
						Right	21	4.53E-01	±	0.21	
					Positive	Left	21	-0.228	±	0.23	
						Midline	21	-0.106	±	0.22	
						Right	21	0.077	±	0.25	
				Posterior	Negative	Left	21	0.037	±	0.22	
						Midline	21	0.393	±	0.27	
						Right	21	0.095	±	0.23	
					Neutral	Left	21	0.037	±	0.22	
						Midline	21	0.393	±	0.27	
						Right	21	0.095	±	0.23	
					Positive	Left	21	0.11	±	0.22	
						Midline	21	0.259	±	0.29	
						Right	21	0.153	±	0.21	
					Negative	Left	21	-0.18	±	0.40	
						Midline	21	-0.157	±	0.33	
						Right	21	0.027	±	0.39	
						Left	21	0.42	±	0.31	

Continued

Appendix 5.10 Continued

Component Mean Amplitudes in Millivolts					Positive	Midline	21	0.259	±	0.29
						Right	21	0.153	±	0.21
	Poorer Regulators	Glucose	Low Demand Encoding	Anterior	Negative	Left	21	-0.18	±	0.40
						Midline	21	-0.157	±	0.33
						Right	21	0.027	±	0.39
					Neutral	Left	21	0.42	±	0.31
						Midline	21	0.25	±	0.20
						Right	21	0.166	±	0.20
					Positive	Left	21	0.109	±	0.42
						Midline	21	0.126	±	0.32
						Right	21	0.045	±	0.36
				Posterior	Negative	Left	21	0.222	±	0.37
						Midline	21	0.568	±	0.37
						Right	21	0.222	±	0.46
					Neutral	Left	21	-0.336	±	0.21
						Midline	21	-0.045	±	0.21
						Right	21	-0.044	±	0.24
					Positive	Left	21	-0.036	±	0.41
						Midline	21	0.02	±	0.52
						Right	21	-0.056	±	0.43
			High Demand Encoding	Anterior	Negative	Left	21	-0.011	±	0.22
						Midline	21	-0.017	±	0.24
						Right	21	-0.262	±	0.31
					Neutral	Left	21	-0.011	±	0.22
						Midline	21	-0.017	±	0.24
						Right	21	-0.262	±	0.31
					Positive	Left	21	-0.488	±	0.57
						Midline	21	-0.253	±	0.34
						Right	21	-0.098	±	0.20
				Posterior	Negative	Left	21	-0.008	±	0.19
						Midline	21	0.245	±	0.22
						Right	21	0.384	±	0.24
					Neutral	Left	21	-0.008	±	0.19
						Midline	21	0.245	±	0.22
						Right	21	0.384	±	0.24
					Positive	Left	21	0.102	±	0.20
						Midline	21	0.346	±	0.25
						Right	21	0.27	±	0.24
		Placebo	Low Demand Encoding	Anterior	Negative	Left	21	-0.218	±	0.36
						Midline	21	0.178	±	0.30
						Right	21	0.152	±	0.38
					Neutral	Left	21	-0.346	±	0.29
						Midline	21	0.057	±	0.24
						Right	21	-0.134	±	0.25
					Positive	Left	21	-0.551	±	0.45
						Midline	21	0.125	±	0.39
						Right	21	0.157	±	0.43
				Posterior	Negative	Left	21	0.056	±	0.34
						Midline	21	0.433	±	0.44
						Right	21	0.308	±	0.41
					Neutral	Left	21	0.289	±	0.27
						Midline	21	0.638	±	0.33
						Right	21	0.499	±	0.27
					Positive	Left	21	-0.049	±	0.30
						Midline	21	0.612	±	0.42
						Right	21	0.674	±	0.42
			High Demand Encoding	Anterior	Negative	Left	21	-0.608	±	0.24
						Midline	21	0.036	±	0.23
						Right	21	0.204	±	0.21
					Neutral	Left	21	-0.608	±	0.24
						Midline	21	0.036	±	0.23
						Right	21	0.204	±	0.21
					Positive	Left	21	0.031	±	0.23
						Midline	21	0.231	±	0.22
						Right	21	0.098	±	0.25
				Posterior	Negative	Left	21	0.198	±	0.22
						Midline	21	0.646	±	0.27
						Right	21	0.771	±	0.23
					Neutral	Left	21	0.198	±	0.22
						Midline	21	0.646	±	0.27
						Right	21	0.771	±	0.23
					Positive	Left	21	-0.066	±	0.22
						Midline	21	0.365	±	0.29
						Right	21	0.267	±	0.21

Appendix 5.11 Word Recognition Old/New Accuracy FN400 component in the 310 to 480 millisecond latency window. Means, SEMs for the 7-way repeated-measures treatment x word type x demand x region x valence x hemisphere x glucoregulation ANOVA. Significant effects and interactions are indicated (Gluc = Glucoregulation, Tr =Treatment, Dem = Demand, Reg = Region, Hem = Hemisphere, Val = Valence, WdTyp = Word Type; (*p<0.05, **p<.005, ***p<.001).

Glucoregulation	Treatment	Word_Type	Demand	Region	Valence	Hemisphere	N	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	Glucose	Old Word	Low Demand Encoding	Anterior	Negative	Left	12	0.372	±	0.58	
						Midline	12	-0.082	±	0.622	
						Right	12	0.412	±	0.483	
					Neutral	Left	12	0.468	±	0.439	
						Midline	12	0.002	±	0.349	Gluc x Tr x WdTyp x Val x Hem *
						Right	12	0.537	±	0.355	
					Positive	Left	12	0.932	±	0.553	
						Midline	12	0.944	±	0.531	Gluc x Tr x WdTyp x Hem *
						Right	12	1.126	±	0.443	
				Posterior	Negative	Left	12	-0.797	±	0.52	
						Midline	12	-1.503	±	0.695	Tr x WdTyp x Hem **
						Right	12	-0.205	±	0.522	
					Neutral	Left	12	-0.951	±	0.42	
						Midline	12	-1.597	±	0.545	WdTyp x Region x Hem ***
						Right	12	-0.172	±	0.41	
					Positive	Left	12	-1.122	±	0.508	
						Midline	12	-1.867	±	0.574	WdTyp x Region ***
						Right	12	-0.515	±	0.505	
			High Demand Encoding	Anterior	Negative	Left	12	0.44	±	0.499	WdTyp x Valence **
						Midline	12	0.343	±	0.492	
						Right	12	0.63	±	0.505	Reg x Hem **
					Neutral	Left	12	0.429	±	0.623	
						Midline	12	0.266	±	0.411	Gluc *
						Right	12	0.796	±	0.423	
					Positive	Left	12	-0.066	±	0.478	Hem ***
						Midline	12	-0.113	±	0.492	
						Right	12	0.2	±	0.551	
				Posterior	Negative	Left	12	-1.343	±	0.525	
						Midline	12	-1.529	±	0.574	
						Right	12	-0.42	±	0.507	
					Neutral	Left	12	-1.475	±	0.504	
						Midline	12	-2.042	±	0.599	
						Right	12	-0.372	±	0.619	
					Positive	Left	12	-1.136	±	0.601	
						Midline	12	-1.74	±	0.607	
						Right	12	-0.435	±	0.421	
		New Word	Low Demand Encoding	Anterior	Negative	Left	12	-0.649	±	0.516	
						Midline	12	-0.839	±	0.48	
						Right	12	-0.093	±	0.419	
					Neutral	Left	12	-0.182	±	0.454	
						Midline	12	-0.505	±	0.373	
						Right	12	0.029	±	0.458	
					Positive	Left	12	-0.64	±	0.397	
						Midline	12	-0.622	±	0.393	
						Right	12	0.31	±	0.427	
				Posterior	Negative	Left	12	-0.419	±	0.422	
						Midline	12	-0.888	±	0.446	
						Right	12	0.401	±	0.45	
					Neutral	Left	12	0.146	±	0.471	
						Midline	12	-1.114	±	0.541	
						Right	12	0.081	±	0.536	
					Positive	Left	12	-0.412	±	0.505	
						Midline	12	-0.96	±	0.633	
						Right	12	0.418	±	0.505	
			High Demand Encoding	Anterior	Negative	Left	12	-0.215	±	0.51	
						Midline	12	-0.792	±	0.495	
						Right	12	0.017	±	0.453	
					Neutral	Left	12	-0.145	±	0.378	
						Midline	12	-0.584	±	0.328	
						Right	12	0.043	±	0.318	
					Positive	Left	12	-0.504	±	0.411	
						Midline	12	-0.999	±	0.388	
						Right	12	-0.31	±	0.429	
				Posterior	Negative	Left	12	-0.64	±	0.543	
						Midline	12	-1.027	±	0.633	
						Right	12	0.066	±	0.506	
					Neutral	Left	12	-0.168	±	0.414	
						Midline	12	-0.946	±	0.419	
						Right	12	0.198	±	0.446	
					Positive	Left	12	-0.323	±	0.396	
						Midline	12	-0.907	±	0.447	
						Right	12	0.573	±	0.357	
	Placebo	Old Word	Low Demand Encoding	Anterior	Negative	Left	12	-0.027	±	0.68	
						Midline	12	-0.246	±	0.689	
						Right	12	0.12	±	0.621	
					Neutral	Left	12	-0.16	±	0.412	
						Midline	12	-0.461	±	0.422	
						Right	12	0.05	±	0.371	
					Positive	Left	12	0.46	±	0.596	
						Midline	12	-0.076	±	0.631	
						Right	12	0.202	±	0.7	
				Posterior	Negative	Left	12	-0.259	±	0.686	
						Midline	12	-1.026	±	0.67	
						Right	12	0.024	±	0.685	
					Neutral	Left	12	-0.37	±	0.438	
						Midline	12	-1.341	±	0.469	
						Right	12	0.047	±	0.501	
					Positive	Left	12	-0.281	±	0.544	
						Midline	12	-1.361	±	0.662	
						Right	12	0.142	±	0.631	
			High Demand Encoding	Anterior	Negative	Left	12	-0.157	±	0.824	
						Midline	12	-0.486	±	0.681	
						Right	12	-0.083	±	0.708	
					Neutral	Left	12	-0.115	±	0.365	
						Midline	12	-0.402	±	0.371	
						Right	12	-0.103	±	0.377	
					Positive	Left	12	0.155	±	0.632	
						Midline	12	0.175	±	0.582	
						Right	12	0.392	±	0.436	
				Posterior	Negative	Left	12	-0.368	±	0.751	
						Midline	12	-1.302	±	0.73	
						Right	12	-0.009	±	0.758	
					Neutral	Left	12	-0.533	±	0.491	
						Midline	12	-1.238	±	0.473	
						Right	12	-0.104	±	0.409	
					Positive	Left	12	-1.215	±	0.477	
						Midline	12	-1.857	±	0.586	
						Right	12	-0.339	±	0.59	
		New Word	Low Demand Encoding	Anterior	Negative	Left	12	-0.625	±	0.384	
						Midline	12	-0.848	±	0.368	
						Right	12	-0.008	±	0.309	
					Neutral	Left	12	-0.882	±	0.514	
						Midline	12	-1.148	±	0.458	
						Right	12	-0.132	±	0.422	
					Positive	Left	12	-0.084	±	0.475	
						Midline	12	-0.2	±	0.478	
						Right	12	0.089	±	0.406	
				Posterior	Negative	Left	12	-0.19	±	0.384	
						Midline	12	-1.196	±	0.473	
						Right	12	0.053	±	0.407	
					Neutral	Left	12	0.262	±	0.483	
						Midline	12	-1.044	±	0.54	
						Right	12	0.441	±	0.529	
					Positive	Left	12	0.076	±	0.497	
						Midline	12	-0.895	±	0.619	
						Right	12	0.086	±	0.619	
			High Demand Encoding	Anterior	Negative	Left	12	-0.284	±	0.572	
						Midline	12	-0.502	±	0.558	
						Right	12	0.09	±	0.469	
					Neutral	Left	12	-0.615	±	0.421	
						Midline	12	-0.679	±	0.404	
						Right	12	0.298	±	0.374	
					Positive	Left	12	-0.263	±	0.54	
						Midline	12	-0.491	±	0.531	
						Right	12	-0.011	±	0.439	
				Posterior	Negative	Left	12	-0.063	±	0.521	
						Midline	12	-1.318	±	0.514	
						Right	12	-0.111	±	0.559	
					Neutral	Left	12	0.058	±	0.479	
						Midline	12	-0.827	±	0.474	
						Right	12	0.366	±	0.469	
					Positive	Left	12	0.137	±	0.508	
						Midline	12	-0.812	±	0.577	
						Right	12	0.333	±	0.525	

Continued

Appendix 5.11 Continued

Poorer Regulators	Glucose	Old Word	Low Demand Encoding	Anterior	Negative	Left	12	0.225	±	0.58
						Midline	12	0.015	±	0.622
						Right	12	0.237	±	0.483
					Neutral	Left	12	-0.663	±	0.439
						Midline	12	-0.542	±	0.349
						Right	12	-0.428	±	0.355
					Positive	Left	12	0.361	±	0.553
						Midline	12	-0.055	±	0.531
						Right	12	-0.179	±	0.443
				Posterior	Negative	Left	12	-0.022	±	0.52
						Midline	12	-0.321	±	0.695
						Right	12	0.909	±	0.522
					Neutral	Left	12	0.144	±	0.42
						Midline	12	-0.203	±	0.545
						Right	12	0.597	±	0.41
					Positive	Left	12	-0.164	±	0.508
						Midline	12	-0.2	±	0.574
						Right	12	0.514	±	0.505
			High Demand Encoding	Anterior	Negative	Left	12	0.184	±	0.499
						Midline	12	0.281	±	0.492
						Right	12	0.274	±	0.505
					Neutral	Left	12	-0.934	±	0.623
						Midline	12	-0.963	±	0.411
						Right	12	-0.714	±	0.423
					Positive	Left	12	-0.735	±	0.478
						Midline	12	-0.474	±	0.492
						Right	12	0.092	±	0.551
				Posterior	Negative	Left	12	-0.519	±	0.525
						Midline	12	-0.575	±	0.574
						Right	12	0.717	±	0.507
					Neutral	Left	12	0.369	±	0.504
						Midline	12	0.03	±	0.599
						Right	12	1.076	±	0.619
					Positive	Left	12	-0.073	±	0.601
						Midline	12	0.075	±	0.607
						Right	12	0.772	±	0.421
		New Word	Low Demand Encoding	Anterior	Negative	Left	12	-0.607	±	0.516
						Midline	12	-0.539	±	0.48
						Right	12	-0.411	±	0.419
					Neutral	Left	12	-1.212	±	0.454
						Midline	12	-0.967	±	0.373
						Right	12	-0.576	±	0.458
					Positive	Left	12	-0.966	±	0.397
						Midline	12	-1.012	±	0.393
						Right	12	-1.408	±	0.427
				Posterior	Negative	Left	12	0.722	±	0.422
						Midline	12	-0.084	±	0.446
						Right	12	0.754	±	0.45
					Neutral	Left	12	0.974	±	0.471
						Midline	12	0.328	±	0.541
						Right	12	1.236	±	0.536
					Positive	Left	12	1.277	±	0.505
						Midline	12	0.858	±	0.633
						Right	12	1.198	±	0.505
			High Demand Encoding	Anterior	Negative	Left	12	-0.95	±	0.51
						Midline	12	-0.829	±	0.495
						Right	12	-0.423	±	0.453
					Neutral	Left	12	-1.469	±	0.378
						Midline	12	-1.191	±	0.328
						Right	12	-0.834	±	0.318
					Positive	Left	12	-0.124	±	0.411
						Midline	12	-0.375	±	0.388
						Right	12	-0.171	±	0.429
				Posterior	Negative	Left	12	0.627	±	0.543
						Midline	12	0.103	±	0.633
						Right	12	1.16	±	0.506
					Neutral	Left	12	1.158	±	0.414
						Midline	12	0.274	±	0.419
						Right	12	1.438	±	0.446
					Positive	Left	12	0.568	±	0.396
						Midline	12	-0.22	±	0.447
						Right	12	0.623	±	0.357
	Placebo	Old Word	Low Demand Encoding	Anterior	Negative	Left	12	0.199	±	0.68
						Midline	12	-0.587	±	0.689
						Right	12	-0.73	±	0.621
					Neutral	Left	12	-0.412	±	0.412
						Midline	12	-0.932	±	0.422
						Right	12	-0.704	±	0.371
					Positive	Left	12	0.516	±	0.596
						Midline	12	-0.398	±	0.631
						Right	12	0.279	±	0.7
				Posterior	Negative	Left	12	0.997	±	0.686
						Midline	12	0.106	±	0.67
						Right	12	1.037	±	0.685
					Neutral	Left	12	0.166	±	0.438
						Midline	12	-0.586	±	0.469
						Right	12	0.662	±	0.501
					Positive	Left	12	-0.291	±	0.544
						Midline	12	-0.661	±	0.662
						Right	12	0.37	±	0.631
			High Demand Encoding	Anterior	Negative	Left	12	-0.087	±	0.824
						Midline	12	-0.244	±	0.681
						Right	12	0.016	±	0.708
					Neutral	Left	12	0.366	±	0.365
						Midline	12	-0.371	±	0.371
						Right	12	-0.196	±	0.377
					Positive	Left	12	0.148	±	0.632
						Midline	12	-0.192	±	0.582
						Right	12	-0.215	±	0.436
				Posterior	Negative	Left	12	0.068	±	0.751
						Midline	12	-0.71	±	0.73
						Right	12	0.186	±	0.758
					Neutral	Left	12	-0.525	±	0.491
						Midline	12	-1.248	±	0.473
						Right	12	-0.169	±	0.409
					Positive	Left	12	0.578	±	0.477
						Midline	12	-0.095	±	0.586
						Right	12	0.949	±	0.59
		New Word	Low Demand Encoding	Anterior	Negative	Left	12	-0.686	±	0.384
						Midline	12	-0.75	±	0.368
						Right	12	-0.406	±	0.309
					Neutral	Left	12	-1.134	±	0.514
						Midline	12	-1.005	±	0.458
						Right	12	-0.368	±	0.422
					Positive	Left	12	-0.871	±	0.475
						Midline	12	-0.579	±	0.478
						Right	12	-0.065	±	0.406
				Posterior	Negative	Left	12	0.7	±	0.384
						Midline	12	-0.494	±	0.473
						Right	12	0.796	±	0.407
					Neutral	Left	12	0.765	±	0.483
						Midline	12	0.231	±	0.54
						Right	12	1.308	±	0.529
					Positive	Left	12	0.615	±	0.497
						Midline	12	-0.043	±	0.619
						Right	12	1.403	±	0.619
			High Demand Encoding	Anterior	Negative	Left	12	-0.584	±	0.572
						Midline	12	-0.384	±	0.558
						Right	12	0.317	±	0.469
					Neutral	Left	12	-1.096	±	0.421
						Midline	12	-0.671	±	0.404
						Right	12	-0.337	±	0.374
					Positive	Left	12	-0.505	±	0.54
						Midline	12	-0.433	±	0.531
						Right	12	0.249	±	0.439
				Posterior	Negative	Left	12	0.101	±	0.521
						Midline	12	-0.346	±	0.514
						Right	12	0.653	±	0.559
					Neutral	Left	12	0.76	±	0.479
						Midline	12	-0.018	±	0.474
						Right	12	1.143	±	0.469
					Positive	Left	12	0.206	±	0.508
						Midline	12	-0.52	±	0.577
						Right	12	0.458	±	0.525

Appendix 5.12 Word Recognition Old/New Accuracy LPC component in the 470 to 780 millisecond latency window. Means, SEMs for the 7-way repeated-measures treatment x word type x demand x region x valence x hemisphere x glucoregulation ANOVA. Significant effects and interactions are indicated (Gluc = Glucoregulation, Tr =Treatment, Dem = Demand, Reg = Region, Hem = Hemisphere, Val = Valence, WdTyp = Word Type; (*p<0.05), **p<0.005, ***P<0.001)

Glucoregulation	Treatment	Word_Type	Demand	Region	Valence	Hemisphere	N	Mean	±	SEM	Significant Effects and Interactions
Better Regulators	Glucose	Old Word	Low Demand Encoding	Anterior	Negative	Left	12	-0.894	±	0.618	
						Midline	12	-0.763	±	0.523	
						Right	12	-0.427	±	0.589	
					Neutral	Left	12	-0.699	±	0.306	
						Midline	12	-0.63	±	0.295	Gluc x Tr x WdTyp x Val x Hem *
						Right	12	-0.795	±	0.257	
					Positive	Left	12	-0.79	±	0.432	Gluc x Tr x WdTyp x Hem *
						Midline	12	-0.936	±	0.405	
						Right	12	-0.728	±	0.452	
				Posterior	Negative	Left	12	1.213	±	0.564	
						Midline	12	1	±	0.68	Tr x WdTyp x Hem **
						Right	12	1.213	±	0.658	
					Neutral	Left	12	1.405	±	0.226	
						Midline	12	1.128	±	0.243	WdTyp x Region x Hem ***
						Right	12	1.073	±	0.323	
					Positive	Left	12	1.721	±	0.348	
						Midline	12	1.467	±	0.305	WdTyp x Region ***
						Right	12	1.339	±	0.414	
			High Demand Encoding	Anterior	Negative	Left	12	-1.007	±	0.395	WdTyp x Valence **
						Midline	12	-0.913	±	0.351	
						Right	12	-1.038	±	0.366	Reg x Hem **
					Neutral	Left	12	-0.967	±	0.312	
						Midline	12	-0.901	±	0.309	Gluc *
						Right	12	-0.972	±	0.324	
					Positive	Left	12	-1.383	±	0.491	Hem ***
						Midline	12	-1.214	±	0.54	
						Right	12	-0.752	±	0.646	
				Posterior	Negative	Left	12	1.461	±	0.345	
						Midline	12	1.474	±	0.33	
						Right	12	1.465	±	0.38	
					Neutral	Left	12	1.258	±	0.344	
						Midline	12	0.839	±	0.367	
						Right	12	1.068	±	0.354	
					Positive	Left	12	1.298	±	0.518	
								1.01		0.496	
						Midline	12	1.485	±	0.598	
						Right	12	-0.972	±	0.391	
		New Word	Low Demand Encoding	Anterior	Negative	Left	12	-0.888	±	0.292	
						Midline	12	-0.951	±	0.345	
						Right	12	-0.371	±	0.358	
					Neutral	Left	12	-0.62	±	0.355	
						Midline	12	-0.54	±	0.323	
						Right	12	-0.934	±	0.438	
					Positive	Left	12	-0.739	±	0.427	
						Midline	12	-0.587	±	0.382	
						Right	12	1.223	±	0.201	
				Posterior	Negative	Left	12	0.822	±	0.301	
						Midline	12	1.181	±	0.284	
						Right	12	0.906	±	0.24	
					Neutral	Left	12	0.442	±	0.309	
						Midline	12	0.842	±	0.329	
						Right	12	0.99	±	0.363	
					Positive	Left	12	0.991	±	0.337	
						Midline	12	1.241	±	0.448	
						Right	12	-0.581	±	0.284	
			High Demand Encoding	Anterior	Negative	Left	12	-0.518	±	0.304	
						Midline	12	-0.297	±	0.312	
						Right	12	-0.298	±	0.347	
					Neutral	Left	12	-0.581	±	0.311	
						Midline	12	-0.469	±	0.337	
						Right	12	-0.949	±	0.309	
					Positive	Left	12	-1.067	±	0.311	
						Midline	12	-0.806	±	0.414	
						Right	12	0.62	±	0.238	
				Posterior	Negative	Left	12	0.518	±	0.32	
						Midline	12	0.851	±	0.403	
						Right	12	0.444	±	0.288	
					Neutral	Left	12	0.102	±	0.398	
						Midline	12	0.499	±	0.431	
						Right	12	1.029	±	0.364	
					Positive	Left	12	0.934	±	0.399	
						Midline	12	1.099	±	0.425	
						Right	12	-0.559	±	0.412	
	Placebo	Old Word	Low Demand Encoding	Anterior	Negative	Left	12	-0.663	±	0.335	
						Midline	12	-0.665	±	0.372	
						Right	12	-0.695	±	0.331	
					Neutral	Left	12	-0.391	±	0.34	
						Midline	12	-0.334	±	0.331	
						Right	12	-1.266	±	0.531	
					Positive	Left	12	-1.292	±	0.469	
						Midline	12	-1.109	±	0.419	
						Right	12	1.44	±	0.396	
				Posterior	Negative	Left	12	1.107	±	0.427	
						Midline	12	0.944	±	0.418	
						Right	12	1.239	±	0.314	
					Neutral	Left	12	1.201	±	0.301	
						Midline	12	1.169	±	0.339	
						Right	12	1.814	±	0.392	
					Positive	Left	12	1.639	±	0.392	
						Midline	12	1.722	±	0.478	
						Right	12	-1.179	±	0.439	
			High Demand Encoding	Anterior	Negative	Left	12	-1.081	±	0.424	
						Midline	12	-0.851	±	0.4	
						Right	12	-0.466	±	0.312	
					Neutral	Left	12	-0.551	±	0.216	
						Midline	12	-0.658	±	0.292	
						Right	12	-1.027	±	0.327	
					Positive	Left	12	-0.876	±	0.285	
						Midline	12	-0.316	±	0.405	
						Right	12	1.453	±	0.372	
				Posterior	Negative	Left	12	1.182	±	0.393	
						Midline	12	1.366	±	0.379	
						Right	12	0.765	±	0.345	
					Neutral	Left	12	0.757	±	0.364	
						Midline	12	0.576	±	0.365	
						Right	12	0.829	±	0.446	
					Positive	Left	12	0.801	±	0.493	
						Midline	12	1.084	±	0.426	
						Right	12	-0.538	±	0.342	
		New Word	Low Demand Encoding	Anterior	Negative	Left	12	-0.561	±	0.327	
						Midline	12	-0.877	±	0.32	
						Right	12	-0.635	±	0.306	
					Neutral	Left	12	-0.729	±	0.263	
						Midline	12	-0.621	±	0.296	
						Right	12	-0.712	±	0.288	
					Positive	Left	12	-0.738	±	0.322	
						Midline	12	-0.707	±	0.292	
						Right	12	1.149	±	0.342	
				Posterior	Negative	Left	12	1.076	±	0.352	
						Midline	12	1.279	±	0.395	
						Right	12	0.825	±	0.291	
					Neutral	Left	12	0.663	±	0.348	
						Midline	12	1.084	±	0.388	
						Right	12	1.003	±	0.308	
					Positive	Left	12	0.771	±	0.292	
						Midline	12	1.075	±	0.353	
						Right	12	-0.27	±	0.281	
			High Demand Encoding	Anterior	Negative	Left	12	-0.434	±	0.32	
						Midline	12	-0.498	±	0.292	
						Right	12	-0.352	±	0.301	
					Neutral	Left	12	-0.349	±	0.285	
						Midline	12	-0.207	±	0.279	
						Right	12	-0.251	±	0.41	
					Positive	Left	12	-0.44	±	0.447	
						Midline	12	-0.205	±	0.392	
						Right	12	0.768	±	0.312	
				Posterior	Negative	Left	12	0.461	±	0.317	
						Midline	12	0.833	±	0.331	
						Right	12	0.517	±	0.275	
					Neutral	Left	12	0.638	±	0.266	
						Midline	12	0.792	±	0.343	
						Right	12	0.581	±	0.325	
					Positive	Left	12	0.399	±	0.347	
						Midline	12	0.818	±	0.462	
						Right	12	-0.059	±	0.618	

Continued

Appendix 5.12 Continued

Poorer Regulators	Glucose	Old Word	Low Demand Encoding	Anterior	Negative	Left	12	-0.03	±	0.523
						Midline	12	0.19	±	0.589
						Right	12	-0.346	±	0.306
					Neutral	Left	12	-0.178	±	0.295
						Midline	12	-0.186	±	0.257
						Right	12	-0.685	±	0.432
					Positive	Left	12	-0.632	±	0.405
						Midline	12	-0.735	±	0.452
						Right	12	0.581	±	0.564
				Posterior	Negative	Left	12	0.604	±	0.68
						Midline	12	1.006	±	0.658
						Right	12	0.685	±	0.226
					Neutral	Left	12	1.088	±	0.243
						Midline	12	1.042	±	0.323
						Right	12	1.387	±	0.348
					Positive	Left	12	1.664	±	0.305
						Midline	12	1.712	±	0.414
						Right	12	-0.779	±	0.395
			High Demand Encoding	Anterior	Negative	Left	12	-0.713	±	0.351
						Midline	12	-0.234	±	0.366
						Right	12	-0.46	±	0.312
					Neutral	Left	12	-0.138	±	0.309
						Midline	12	-0.046	±	0.324
						Right	12	-0.419	±	0.491
					Positive	Left	12	-0.194	±	0.54
						Midline	12	0.049	±	0.646
						Right	12	0.636	±	0.345
				Posterior	Negative	Left	12	0.829	±	0.33
						Midline	12	1.51	±	0.38
						Right	12	0.572	±	0.344
					Neutral	Left	12	0.827	±	0.367
						Midline	12	1.031	±	0.354
						Right	12	0.401	±	0.518
					Positive	Left	12	0.502	±	0.496
						Midline	12	0.988	±	0.598
						Right	12	-0.496	±	0.391
		New Word	Low Demand Encoding	Anterior	Negative	Left	12	-0.321	±	0.292
						Midline	12	-0.23	±	0.345
						Right	12	-0.759	±	0.358
					Neutral	Left	12	-0.338	±	0.355
						Midline	12	-0.322	±	0.323
						Right	12	-0.061	±	0.438
					Positive	Left	12	-0.069	±	0.427
						Midline	12	0.143	±	0.382
						Right	12	0.587	±	0.201
				Posterior	Negative	Left	12	0.616	±	0.301
						Midline	12	1.288	±	0.284
						Right	12	0.843	±	0.24
					Neutral	Left	12	1.18	±	0.309
						Midline	12	1.427	±	0.329
						Right	12	0.286	±	0.363
					Positive	Left	12	0.366	±	0.337
						Midline	12	0.56	±	0.448
						Right	12	-0.306	±	0.284
			High Demand Encoding	Anterior	Negative	Left	12	0.007	±	0.304
						Midline	12	-0.105	±	0.312
						Right	12	-0.208	±	0.347
					Neutral	Left	12	-0.023	±	0.311
						Midline	12	0.1	±	0.337
						Right	12	-0.337	±	0.309
					Positive	Left	12	-0.486	±	0.311
						Midline	12	-0.355	±	0.414
						Right	12	0.783	±	0.238
				Posterior	Negative	Left	12	1.021	±	0.32
						Midline	12	1.208	±	0.403
						Right	12	0.337	±	0.288
					Neutral	Left	12	0.597	±	0.398
						Midline	12	1.114	±	0.431
						Right	12	0.325	±	0.364
					Positive	Left	12	0.307	±	0.399
						Midline	12	0.977	±	0.425
						Right	12	-1.285	±	0.412
	Placebo	Old Word	Low Demand Encoding	Anterior	Negative	Left	12	-0.796	±	0.335
						Midline	12	-0.391	±	0.372
						Right	12	-0.803	±	0.331
					Neutral	Left	12	-0.464	±	0.34
						Midline	12	-0.326	±	0.331
						Right	12	-0.385	±	0.531
					Positive	Left	12	-0.275	±	0.469
						Midline	12	-0.058	±	0.419
						Right	12	1.426	±	0.396
				Posterior	Negative	Left	12	1.601	±	0.427
						Midline	12	1.957	±	0.418
						Right	12	0.97	±	0.314
					Neutral	Left	12	1.226	±	0.301
						Midline	12	1.435	±	0.339
						Right	12	0.801	±	0.392
					Positive	Left	12	0.913	±	0.392
						Midline	12	0.964	±	0.478
						Right	12	-1.134	±	0.439
			High Demand Encoding	Anterior	Negative	Left	12	-0.524	±	0.424
						Midline	12	-0.36	±	0.4
						Right	12	-0.629	±	0.312
					Neutral	Left	12	-0.578	±	0.216
						Midline	12	-0.47	±	0.292
						Right	12	-0.603	±	0.327
					Positive	Left	12	-0.368	±	0.285
						Midline	12	-0.482	±	0.405
						Right	12	1.287	±	0.372
				Posterior	Negative	Left	12	1.386	±	0.393
						Midline	12	1.47	±	0.379
						Right	12	0.619	±	0.345
					Neutral	Left	12	0.635	±	0.364
						Midline	12	1.117	±	0.365
						Right	12	1.531	±	0.446
					Positive	Left	12	1.362	±	0.493
						Midline	12	1.609	±	0.426
						Right	12	-0.347	±	0.342
		New Word	Low Demand Encoding	Anterior	Negative	Left	12	-0.27	±	0.327
						Midline	12	-0.139	±	0.32
						Right	12	-0.327	±	0.306
					Neutral	Left	12	-0.112	±	0.263
						Midline	12	-0.074	±	0.296
						Right	12	-0.731	±	0.288
					Positive	Left	12	-0.809	±	0.322
						Midline	12	-0.536	±	0.292
						Right	12	0.708	±	0.342
				Posterior	Negative	Left	12	0.322	±	0.352
						Midline	12	0.9	±	0.395
						Right	12	0.449	±	0.291
					Neutral	Left	12	0.683	±	0.348
						Midline	12	1.058	±	0.388
						Right	12	0.848	±	0.308
					Positive	Left	12	0.836	±	0.292
						Midline	12	1.49	±	0.353
						Right	12	-0.203	±	0.281
			High Demand Encoding	Anterior	Negative	Left	12	-0.098	±	0.32
						Midline	12	-0.175	±	0.292
						Right	12	-0.243	±	0.301
					Neutral	Left	12	-0.278	±	0.285
						Midline	12	-0.087	±	0.279
						Right	12	-0.282	±	0.41
					Positive	Left	12	-0.075	±	0.447
						Midline	12	0.028	±	0.392
						Right	12	0.559	±	0.312
				Posterior	Negative	Left	12	0.524	±	0.317
						Midline	12	1.014	±	0.331
						Right	12	0.519	±	0.275
					Neutral	Left	12	0.341	±	0.266
						Midline	12	0.676	±	0.343
						Right	12	0.211	±	0.325
					Positive	Left	12	0.643	±	0.347
						Midline	12	1.049	±	0.462
						Right	12	0.458	±	0.525