COGNITIVE AND BRAIN FUNCTION IN ADULTS WITH TYPE 1 DIABETES MELLITUS: IS THERE EVIDENCE OF ACCELERATED AGEING?

Harriet N. Johnston

A Thesis Submitted for the Degree of PhD
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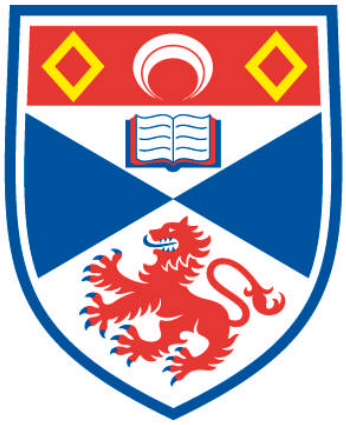
University of St Andrews



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Submitted for the degree of Doctor of Philosophy

University of St Andrews

September 2012

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I, Harriet N. Johnston hereby certify that this thesis, which is approximately 71.000 words in length, has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree.

I was admitted as a research student in September 2008 and as a candidate for the degree of Ph.D. in September 2008; the higher study for which this is a record was carried out in the University of St Andrews between 2008 and 2012.

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Abstract

The physical complications of Type 1 diabetes mellitus (T1DM) have been understood as an accelerated ageing process (Morley, 2008). Do people with T1DM also experience accelerated cognitive and brain ageing? Using findings from research of the normal cognitive and brain ageing process and conceptualized in theories of the functional brain changes in cognitive ageing, a combination of cognitive testing and functional magnetic resonance imaging (fMRI) techniques were used to evaluate evidence of accelerated cognitive and brain ageing in middle-aged adults with T1DM.

The first part of this thesis comprises a cognitive study of 94 adults (≥ 45 years of age) with long duration (≥ 10 years) of T1DM. Participants completed cognitive assessment and questionnaires on general mood and feelings about living with diabetes. Findings highlighted the importance of microvascular disease (specifically retinopathy) as an independent predictor of cognitive function. The incidence and predictors of mild cognitive impairment (MCI) were then explored. Results indicate a higher percentage of the group met criteria for MCI than expected based on incidence rates in the general population, providing initial evidence of accelerated cognitive ageing. Psychological factors were explored next. The relationship between the measures of well-being, diabetes health, and cognitive function highlighted the need for attention to patient's psychological well-being in diabetes care. Finally, a subgroup of 30 participants between the

ages of 45 and 65 who differed on severity of retinopathy were selected to take part in an fMRI study. Blood oxygen level dependent (BOLD) activity was evaluated while participants were engaged in cognitive tasks and during rest. The findings provided evidence that the pattern of BOLD activation and functional connectivity for those with high severity of retinopathy are similar to patterns found in adults over the age of 65. In line with the theories of cognitive ageing, functional brain changes appear to maintain a level of cognitive function. Evidence of accelerated brain ageing in this primarily middle-aged group, emphasizes the importance of treatments and regimens to prevent or minimize microvascular complications.

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Chapter 1
INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a chronic metabolic condition that commonly develops in childhood or adolescence. The physical complications of T1DM are well documented. What is less well understood is the heightened risk of cognitive dysfunction associated with T1DM. In this thesis I investigate the diabetes health predictors of cognitive and brain function in middle-aged and older adults with T1DM. The aim is to understand how and why T1DM affects cognitive and brain function, which aspects are most vulnerable and how this relates to cognitive and brain function in normal ageing.

1.1. Type 1 Diabetes Mellitus

Diabetes affects almost 1 in 20 people in the U.K. population, with 2.8 million people diagnosed (Diabetes UK, 2011a) and estimates of this number rising up to 4 million by 2025 (Diabetes UK, 2010). T1DM affects 10% of people with diabetes, approximately 1 in 700 to 1000, and it is also on the rise (Diabetes UK, 2010). TIDM is a disorder that occurs when the body is unable to produce insulin. This happens when insulin-producing beta cells in the pancreas are destroyed by the body's immune system leading to a disruption in the body's ability to use glucose that is present in the blood.

People with T1DM need to administer insulin and maintain a careful balance between eating and exercise to keep blood glucose values near normal levels. This is referred to as maintaining glycaemic

control, which is essential for preventing extremes of low blood glucose (*hypo*glycaemia) and high blood glucose (*hyper*glycaemia) and related complications. In the course of treatment, a patient's glycaemic control is tested through the HbA1c value. This is a measure of glycosylated hemoglobin level, a product of glucose binding to hemoglobin in red blood cells. The higher an individual's blood glucose level, the more HbA1c is produced, and the higher percentage value of HbA1c (Michigan Diabetes Research and Training Center, 2009). The HbA1c value is affected by glucose levels over an 8 to 12 week period and is an established predictor for diabetes complications (Nathan, Turgeon, & Regan, 2007). The target HbA1c value for individuals with T1DM is 6.5% an HbA1c level at 8.5% or above is considered high (Diabetes UK, 2009).

The brain requires a constant supply of glucose to function (McCall, 2004). As a result, acute hypoglycaemia causes immediate impairment of brain function and cognitive processing (McAulay, Deary, Sommerfield, & Frier, 2006; Sommerfield, McAulay, Deary, & Frier, 2003; Strachan, Ewing, Frier, McCrimmon & Deary, 2003). There is also some evidence that normal cognitive function is disrupted when there is an overload of glucose available, or acute hyperglycaemia (Cox et al., 2005). In the long term, hyperglycaemia causes damage to small blood vessels (microvascular diseases) that can damage the eyes (retinopathy) kidneys (nephropathy) and peripheral nerves (neuropathy; Diabetes UK, 2010). Individuals with T1DM are also at elevated risk of damage to large blood vessels (atherosclerosis)

leading to an increased risk of early onset of hypertension, heart disease and stroke, (Morley, 2008).

1.2. Accelerated Ageing in T1DM

The physical changes due to hyperglycaemia have been characterized as an accelerated ageing process (Morley, 2008). This process is related to increasing levels of blood glucose (McNay, 2005), but other factors are also important (Cheitlin, 2003) including insulin resistance, dyslipidaemia, hypertension, and arterial stiffness (Aronson, 2003; O'Rourke & Hashimoto, 2007). Given the accelerated physiological ageing in T1DM (Aronson, 2003) it may be possible to observe signs of accelerated cognitive ageing in middle-age groups with T1DM.

There is little research available focused on older adults with T1DM, and limited information available about cognitive ageing in this group. What research does exist shows the same primary areas of cognitive processing deficits that have been identified in research with younger adults (Brands et al., 2006), specifically processing speed and cognitive flexibility (switching between tasks). On tasks involving information processing speed, older adults showed greater cognitive decline prospectively than controls (Van Duinkerken et al., 2011), and weaker performance compared with controls (Brands et al., 2006).

There is some debate over the evidence of accelerated cognitive ageing in T1DM. Ryan, Geckle, and Orchard (2003) found a significant decline in psychomotor speed over a relatively short period of time (7 years) in young to middle age adults (age 18-55) with no

corresponding decline in a control group, suggesting early decline in this particular area. However, in his comparison of older and younger groups with T1DM, Ryan (2005) argues that he found no evidence for accelerated cognitive ageing because he only found early cognitive decline in the area of processing speed and the rate of decline was not steeper for older adults in comparison to younger adults. Although in a more recent review of the lieterature, the similarities between the normal ageing process and the pattern of cognitive deficits identified in adult groups with T1DM have been emphasized (Brands, Kessels, & Ryan, 2009).

Park & Reuter-Lorenz (2009) indicate that the cognitive processes most often implicated in normal ageing are working memory (short-term storage and mental manipulation of information), executive function (inhibition of one thought/action to follow another) and processing speed (time to complete a simple cognitive task). Given that processing speed is one of the key deficits identified in the normal ageing process, it could be that cognitive processing within the T1DM group is a sign of accelerated cognitive ageing and decline in these processes may be mitigated by functional brain changes that have not been investigated in earlier studies of cognition in T1DM.

1.3. Mild Cognitive Impairment and Diabetes

Another indicator of accelerated cognitive ageing would be a heightened and/or earlier incidence of mild cognitive impairment (MCI). MCI is generally defined by memory or other cognitive impairments out of the normal range for age, with preserved

functioning with respect to age in general cognitive function, with problems noticeable to the person themselves and others, however these problems do not significantly impact daily functioning (Chertkow et al., 2008; Petersen, 2004; Gauthier et al., 2006). In some studies of T1DM, the incidence of MCI was not higher in those with and without diabetes, however the presence of MCI was associated with longer duration, insulin treatment, younger age of onset and diabetes complications (Roberts et al., 2008). In adults over age 65, Type 2 diabetes was associated with a 1.4 times higher risk of MCI than for those without diabetes (Luchsinger et al., 2007). Some studies noted a particular deficit in processing speed in the nature of the MCI noted in the diabetes population (Arvanitakis, Wilson, Bienias, Evans, & Bennett, 2004; Toro, Schonknecht, & Schroder, 2009), however others have reported that memory type (amnestic) MCI is more prevalent than non-amnestic types of MCI when controlling for factors such as years of education (Luchsinger et al., 2007). It has also been found that older adults (over age 50) with T1DM indicate more subjective cognitive complaints than those without diabetes of the same age (Brands et al., 2006). Other researchers (Brismar et al., 2007) have also found a high level of participants reporting a subjective experience of cognitive decline (39%) even in a relatively younger group with T1DM (mean age = 43.3). A higher incidence of MCI compared to the normal population would provide support of an accelerated cognitive ageing process in T1DM.

1.4. Psychological Variables

People with T1DM need to administer insulin and maintain a careful balance between eating and exercise to keep blood glucose values near normal levels. With much of the treatment of those with diabetes reliant on optimal self-management, psychological variables like anxiety, depression and general well being may impact on the effective management of diabetes, overall health, and likelihood of developing microvascular complications. Depression or other emotional factors may then have a negative impact on control and have an indirect influence on the incidence of microvascular complications (Lustman & Clouse, 2005; Shaban, Fosbury, Cavan, Kerr, & Skinner, 2009). It is important to take psychological variables into account given the link with control and microvascular disease. Positive psychological characteristics could be one factor that contributes to better outcomes through the cognitive ageing process.

1.5. Functional Brain Imaging in Type 1 diabetes

Before a case for accelerated ageing can be made or definitively ruled-out, it is necessary to investigate what is happening functionally within the brains of indiviuduals with T1DM to sustain cognitive processing. To date, functional imaging has been used infrequently in the study of cognitive function in T1DM. Results of these studies indicate a pattern of altered brain activation for individuals with T1DM and retinopathy indicating less task-related deactivation sites associated with resting state (Wessels et al., 2006) and less connectivity in resting state (Van Duinkerken et al, 2011).

Neuroimaging studies have revealed some structural differences between groups of individuals with T1DM, but these are not often areas indicated through cognitive testing. Functional MRI is ideal because it links cognitive performance and brain function and can answer the question of whether there is evidence of accelerated ageing in adults with T1DM.

1.6. Study Aims and Questions

1.6.1. Cognitive Study

The aim of the cognitive study was to determine whether there is evidence of cognitive processing issues in groups who differ on diabetes health variables or general health variables and whether these differences could be considered signs of accelerated ageing within these subgroups. Comparing the outcomes for those with T1DM and diabetes health variables (e.g., chronic hyperglycaemia, greater microvascular disease, recurrent severe hypoglycaemia) to those with T1DM and optimal health provides an indication of factors that differentiate group performance. Understanding the relationship of these factors to cognitive processing can help determine interventions that may promote maintenance of cognitive function in ageing. The strongest diabetes health predictor of cognitive function that emerged from the cognitive study was used in creating comparison groups for the neuroimaging study as this factor was considered most likely to have influence on brain function within this group.

1. Do individuals who differ on diabetes health variables (e.g., glycaemic control, microvascular complications) show significantly different scores on measures of cognitive processes?
2. Is cognitive function related to general health variables and health promoting habits (e.g. BMI, blood pressure, cholesterol, exercise, cognitive activity)?
3. Which diabetes health variables have the strongest predictive value on cognitive function?

1.6.2. Mild Cognitive Impairment

Although diagnosed MCI was an exclusion criteria for the cognitive study, there were some individuals who showed significant cognitive deficits on tests used in the cognitive study. The aim of this study was to determine the incidence and predictors of MCI. This was used as an initial technique to determine the evidence of early cognitive ageing in this group with T1DM. High incidence of MCI in middle-aged adults was regarded as evidence of early cognitive ageing in this group.

1. What is the incidence and nature of MCI in the study sample? How does this compare to the incidence of MCI the general population?
2. Are there differences in the age, education or general intelligence of the participants in the study sample who show MCI in comparison to those who show lower levels of cognitive impairment?

3. Are there differences in general health variables and health habits in those who show MCI in comparison to those who show lower levels of cognitive impairment?
4. Are there differences in diabetes health variables for those with MCI and in comparison to those who show lower levels of cognitive impairment? What are the strongest predictors of MCI?

1.6.3. Psychological Variables

The aim of the investigation of psychological variables was to determine whether measures of well-being (e.g., anxiety, depression) relate to diabetes health variables and cognitive function and what this relationship could suggest in optimizing positive outcomes for individuals with T1DM. Identification of potential modifiable factors may provide targets for promoting maintenance of cognitive function in ageing.

1. What percentage of the study group are classified within each category on the HADS anxiety and depression scale?
2. Do measures of well-being relate to demographic variables?
3. Do measures of well-being relate to diabetes health variables?
4. Do measures of well-being relate to cognitive function?

1.6.4. Neuroimaging Study

The aim of the functional neuroimaging study was to determine whether there were notable differences in brain function between groups with low and high severity of diabetes microvascular complications that may suggest early brain ageing in this group. Use

of functional brain imaging provides the ability to determine whether cognitive function in groups with greater microvascular complications is maintained by brain function typically identified in ageing groups, providing evidence of accelerated ageing.

1. Does neural activation (as indicated by the blood oxygen level dependent (BOLD) response in fMRI), when completing a cognitive task and at rest, differ between groups with high severity retinopathy and those with low severity retinopathy?
2. Does BOLD activation in the high severity retinopathy group resemble patterns found in normal ageing?

1.7. Thesis Outline

Although cognitive changes are expected within the normal ageing process, chronic disease can also have an influence on these cognitive and brain changes. The study of cognitive ageing in T1DM provides the opportunity to investigate the impact of different disease variables within a group that has had long-standing chronic disease and to evaluate evidence of accelerated ageing. The inclusion of personal characteristics and psychological variables provides a focus on protective and modifiable factors that is typically not included in T1DM research and can inform recommendations that help preserve cognitive function in ageing.

This thesis examines cognitive and brain function in middle age to older adults with T1DM who differ on aspects of diabetes and to determine whether there is evidence of early cognitive and brain ageing within this group and the identification of modifiable protective factors

of cognitive function in ageing. Initially, cognitive testing was used to investigate the relationship of long-term glycaemic control, diabetes complications (e.g. microvascular diseases), as well as general health variables and health promoting habits on cognitive performance. This was followed by an examination of the incidence, nature and predictors MCI in the study group. Next, the influence of general and diabetes specific well-being were examined in their influence on diabetes health variables. Finally, functional neuroimaging techniques were used to determine whether signs of accelerated brain ageing could be identified in individuals with and without microvascular disease.

Chapter 2 provides an overview of research and theory related to the normal cognitive ageing process. Chapter 3 provides detailed information on the cognitive processes that appear to be most affected in T1DM and within the normal cognitive ageing process. These are the cognitive processes that are a focus of this thesis. This chapter also includes information on the relationship of these cognitive processes diabetes complications These are the key diabetes health variables used in the cognitive study and the investigation of MCI. The final part of the chapter provides a review of the psychological factors that may influence self-management and mitigate the diabetes complications that have been related to the cognitive processing deficits identified in groups with T1DM and are the focus of the study of psychological variables.

The studies undertaken for this thesis are described in the following chapters. Details of the participant group and recruitment are

provided in Chapter 4. The cognitive study is described in Chapter 5. In this study, a clinic sample of self-referred middle aged and older adults with T1DM were asked to complete a battery sampling various cognitive processes along with a questionnaire regarding health habits and diabetes history and well-being questionnaires. This chapter concerns the identification of the strongest diabetes health predictors of cognitive function and cognitive change to determine those most likely to impact functional brain ageing. Chapter 6 is a closer investigation of the sub-group within the sample that met criteria for the identification of MCI. This includes comparison to the UK incidence statistics and identification of predictors of MCI in the study group. In Chapter 7, an investigation of the relationship between personal and psychological factors on diabetes and general health variables is explored.

A functional MRI study, is presented in Chapter 8. In this neuroimaging study a subgroup of 30 people, who took part in the cognitive study, completed functional magnetic resonance imaging scans of the brain. Based on results of the cognitive study and MCI investigation that microvascular disease (retinopathy) was most consistently predictive of cognitive function, participants were placed in two groups, those with low severity of retinopathy and those with high severity of retinopathy. Brain function was compared when completing cognitive tasks and in resting state between these groups and compared with results of research in normal ageing populations.

Finally, Chapter 9 provides a general discussion of the conclusions of the two studies in the thesis evaluating the evidence for accelerated ageing in middle aged and older adults with T1DM and the potential factors that could protect cognitive function through the ageing process.

Chapter 2
Cognitive Ageing

2.1. Cognitive Ageing in Healthy Adults

The cognitive ageing process affects, "people's abilities to activate, to represent and maintain information in mind, to attend to relevant but ignore irrelevant information, and to process information promptly" (Li, Lindenberger, & Sikström, 2001, p. 479). Results of research on normal cognitive ageing indicate that abilities in different cognitive domains deteriorate at different rates. Some cognitive functions such as processing speed begin to deteriorate early in adulthood and others, such as verbal knowledge, remain intact into late adulthood. In his cross-sectional studies, Salthouse (2004) found that several cognitive processes including immediate verbal memory, processing speed, and fluid reasoning decreased steadily from the early twenties. In contrast, he found that crystallized intelligence peaked in the forties or fifties and remained stable until the 70s. It is thought that weakening processing efficiency places limits on the expression of both fluid and crystallized intelligence (Li et al., 2004).

Results of the Seattle Longitudinal Study on ageing indicate that decrease in functioning in certain domains foreshadow cognitive impairment by showing earlier decline (Willis & Schaie, 2005). These include immediate and delayed verbal recall, word fluency and psychomotor speed. They found that greater decline of these domains in midlife was an effective indicator of future cognitive impairment.

Brain structure also changes with age along with changes in cognitive performance seen in ageing. The structural brain imaging research of Sowell and colleagues (2003) supports findings from longitudinal cognitive ageing research. These researchers found that between the ages of 7 and 60 there is a decrease in gray matter density in dorsal frontal, parietal lobes, and orbitofrontal cortex that was accompanied by increases in white matter volume until age 40. They suggest that this pattern indicates a trade off between gray matter volume and myelination of white matter tracks until this time. After age 40 there is a neurodegenerative process with a corresponding decrease in brain weight and increase in volume of cerebral spinal fluid. The temporal lobes show a gain in gray matter until the 30s and stay stable, only declining in old age, which is consistent with the findings for maintenance of crystallized intelligence and vocabulary skills well into late adulthood.

2.2. Theories of Cognitive Ageing

Although brain insults and structural changes occur in the normal ageing process, cognitive performance may be maintained well for some individuals. Two theories that provide explanatory models include Cognitive Reserve (Stern, 2002) and Scaffolding Theory of Ageing and Cognition (STAC; Park & Reuter-Lorenz, 2009).

2.2.1. Cognitive Reserve (CR)

In the cognitive reserve (CR) model, Stern (2002) suggests that the brain adapts to damage through both cognitive processing strategies

and compensation. It is hypothesized that the higher CR of an individual, the higher threshold for adapting to brain insults and maintaining cognitive performance. In this way the same brain pathology may lead to different cognitive outcomes for different individuals with more or less cognitive reserve. Tucker and Stern (2011) maintain that CR is not a fixed characteristic and that the more modifiable factors have independent and combined positive impact on CR even when introduced later in life. Increased cognitive reserve can be measured by a number of inate and modifiable factors including higher intelligence quotient (IQ), professional occupation level, socio-economic status, literacy, educational attainment, exercise, leisure activities, social experiences and cognitive engagement. It is hypothesized that two neural processes underly CR, neural reserve and neural compensation (Stern, 2009). Neural reserve is the use of neural networks for cognitive processing that have more sustainability, are more efficient, and have more capacity to deal with damage or demands. Neural compensation is the use of alternate brain networks for cognitive processing not usually used to compensate for brain damage. This is supported by research showing that some individuals can have more Alzheimer's Disease (AD) pathology in the brain and appear cognitively similar to individuals with less AD pathology and the differences observed in the brain networks used by younger and older adults to obtain the same performance on a cognitive task (Stern, 2006; Stern, 2009).

2.2.2. Scaffolding Theory of Ageing and Cognition (STAC)

Even though a number of cognitive processing abilities are changing, alterations in brain function are believed to compensate for these changes. Through the Scaffolding Theory of Ageing and Cognition (STAC), Park and Reuter-Lorenz (2009) argue that cognitive ageing occurs through a combination of neurocognitive declines and compensatory neural mechanisms, which are predictive of cognitive function. In ageing, scaffolding includes the functional brain changes that promote and preserve optimal cognitive function. They believe that the ageing process is adaptive, allowing us to maintain our daily functioning and independence even though a number of our cognitive processing abilities are changing (Park & Reuter-Lorenz, 2009). According to the Park and Reuter-Lorenz (2009), greater degrees of functional brain ageing can occur due to some chronic diseases. The STAC theory suggests that middle-aged adults who show signs of pervasive scaffolding are at risk of early decline in cognitive performance. This may manifest in greater incidence and earlier onset of mild cognitive impairment (MCI) an intermediate stage between normal cognitive ageing and dementia, characterized by cognitive processing significantly below age expectations, often in the area of memory. Functional neuroimaging studies suggest particular patterns evident in ageing. These patterns differentiate older adults from younger adults and support cognitive function in ageing. These include over-activation in frontal regions, lack of deactivation in areas associated with rest (i.e., default mode network) when there are

increasing task demands and less connectivity between regions when at rest (Reuter-Lorenz & Park, 2010).

2.3. Summary

The cognitive impairments common in normal ageing (deficits in processing speed, working memory, and inhibition) are mediated by structural and functional brain changes. Two complementary theories that are used to understand the maintenance of cognitive performance despite brain damage related to aging or disease. Both CR and STAC indicate that there are neural networks that compensate for brain insults. CR places emphasis on the inate and modifiable factors that can be used to predict better cognitive outcomes and the relation with higher neural reserve. STAC focuses on the scaffolding processes, or functional changes themselves and how these compensatory mechanisms can be enhanced. Both theories suggest that outcomes in cognitive ageing are not fixed and can be influenced through modifiable factors across the lifespan. Both of these theories provide an understanding of how cognitive processes can be maintained through functional brain changes and modified through lifestyle choices. Looking at the cognitive performance and brain function through the lens of cognitive ageing is important to determine whether ageing in the T1DM population appears the same, accelerated, or on a unique path to that described in research and theories of healthy cognitive ageing.

Chapter 3
COGNITIVE PROCESSES AND DIABETES HEALTH VARIABLES

3.1. Cognitive Processes Identified in T1DM Research

A meta-analysis of large group studies has revealed that individuals with T1DM show mild to moderate deficits in certain cognitive domains in comparison to control groups without diabetes (Brands et al., 2005). These include crystallized and fluid intelligence, psychomotor efficiency, cognitive flexibility, sustained attention, and selective attention. Other areas were not significantly affected including verbal learning and memory, working memory and language. Brands and colleagues (2005) suggest that the lower scores in crystallized and fluid intelligence reflected impairments in primary mental abilities including efficiency and flexibility, rather than a deficit in general intelligence per se. Since this review was published, further studies have also shown a specific deficit in psychomotor efficiency and cognitive flexibility for those with T1DM (Brismar et al., 2007; Jacobson et al., 2007; Ryan, 2005).

The studies of cognition it T1DM have mainly focused on adults under the age of 50 (Brands et al., 2005). Results of available research regarding older adults are inconclusive. Only small groups have been studied primarily representing a healthy group in the Netherlands. Brands and colleagues (2006) studied group of 40 individuals with T1DM. Although they found a trend for relative deficits in all

cognitive domains, the T1DM group only showed a significant difference in psychomotor efficiency and cognitive flexibility, the same areas typically found in the T1DM research with younger adults. They also determined that the level of brain abnormalities were in the normal range for age. They concluded that although this older group with T1DM did somewhat worse on all cognitive tasks, it was not significant and not related to any structural brain changes. They suggested that because their sample drew from a particularly well-controlled cohort in terms of glucose management, that these factors might have diminished the potential to find any other differences between the group with T1DM and control groups. In a prospective study of the same sample, only on tasks involving information processing speed did older adults show greater cognitive decline prospectively than controls (Van Duinkerken et al., 2011).

There has also been one study from the United States, with a small sample of middle-aged adults. Ryan (2005) directly compared a cohort of individuals with T1DM and controls over a wide age range (18 to 64) to address the question of whether cognitive changes in the group with diabetes resembled that of cognitive ageing. He concluded that the answer was no because cognitive impairments for this group were primarily in the area of "psychomotor slowing" rather than across cognitive domains.

3.1.1. Description of Cognitive Processes

The following is an overview of the key cognitive processes identified in T1DM research along with the neuropsychological tests

commonly used to assess function in these areas. These cognitive processes will be included in the cognitive study test battery. The cognitive battery used in this thesis covers all the cognitive processes and tests identified in this chapter. More specific details of the cognitive battery are provided in Chapter 4.

Fluid and Crystallized Intelligence

Intelligence has been traditionally conceptualized in terms of a contrast between fluid problem solving ability and crystallized knowledge. Cattell (1971) classifies fluid intelligence as inductive and deductive reasoning abilities with biological and neurological underpinnings affected by incidental learning determined by the environment. In contrast crystallized intelligence consists of acquired knowledge resulting from cultural experiences. The Raven's Progressive Matrices is a common measure of fluid intelligence and vocabulary or general knowledge tests are measures of crystallized intelligence (Deary, Whalley, & Crawford, 2004). Given that crystallized intelligence is stable into later adulthood, these types of tests are used to estimate a person's past intellectual ability. Premorbid intelligence is an estimate or actual baseline cognitive function before disease or injury. Evidence from studies on the Scottish Mental Survey cohorts indicated a high correlation between a common test of premorbid intelligence, the National Adult Reading Test (NART) and intelligence tested at age 11(Crawford, Deary, Starr, & Whalley, 2001).

Processing Speed

Processing speed is a multifaceted cognitive domain that encompasses many subdomains. There have been six distinct types of speed measures identified by Salthouse (2000). Some include a measure of time to complete a task, and others focus on the number of items completed within a time limit. These vary in the relative difficulty of the cognitive task and the complexity of the motor response. Three distinctions from Salthouse (2000) are helpful in understanding past cognitive research with T1DM groups and the cognitive tasks used in the current study. These include psychomotor speed, perceptual speed, and psychophysical speed. These are summarized in Table 3.1. The tasks of processing speed used in the cognitive study, Symbol Digit Modalities and Trail Making Test A, are types of perceptual speed tasks according to Salthouse's (2000) distinction. Measures of perceptual speed have been related to decision accuracy rather than time working on a problem or time to make the response (Salthouse, 2000). Across this variety of different measures, processing speed has a strong relation with age (Salthouse, 2000). The processing speed task used in the neuroimaging study, inspection time, is a psychophysical speed task. The processing speed tasks used by some researchers are psychomotor speed tasks with a more complex motor component, such as the grooved pegboard test used in a study by Ryan (2005).

Table 3.1 *Summary Of Three Types Of Processing Speed Tasks Used In T1DM Research And The Current Study (Salthouse, 2000).*

Processing Speed Task	**Test Type**	**Measurement**	**Cognitive Difficulty**	**Motor Difficulty**
Psychomotor Speed	Repetitive motor movement or manipulation	Time to complete a motor task	Simple – performance perfect	Moderate – dependent on dexterity, hand-eye coordination
Psycho-physical Speed	Discrimination between visual or auditory stimuli presented for under one second	Correct Responses to barely perceivable visual or auditory stimulus	Simple – perfect if stimulus on for long enough	Simple – button press
Perceptual Speed	Visual search for matching items, completing items using a code,	Correct responses within a time limit to simple content	Simple – perfect if no time limit	Simple – paper and pencil

Executive Function

Executive functions encompass a number of related processes. Royall and colleagues (2002) define executive functions as a "set of cognitive skills responsible for planning, initiating, sequencing and

monitoring of complex goal-directed behaviour" (p. 378). Miyake and colleagues (2000), indicate that the three most studied executive functions include "shifting mental set, monitoring and updating working memory, and inhibition of preponent responses" (p. 50) which they consider lower level executive functions that underlie more complex executive functions such as planning.

Brands and colleagues (2005) defined cognitive flexibility as the ability to shift concepts and problem-solving strategies, fitting with the definition of an executive function task, and found that this was a key area of cognitive deficit in T1DM. These tasks require set shifting or switching from one mode of response to another or determining changes in task rules. The executive task used in this study, Trail Making Test B (TMT-B; Army Individual Test Battery, 1944), requires the participant to switch focus between numbers and letters as quickly as possible.

3.1.2. Critique of Cognitive Tests used in T1DM Research

The conclusions of recent research in this area are uncertain due to choices of tests for certain cognitive domains. For example, Brismar and colleagues (2007) found a broader array of cognitive domains to be deficient in individuals with T1DM than some other researchers have (Ryan, 2005). However, several of the tests or combinations of tests overlap on two or three domains. For example Trail Making B is included as a measure of executive function, information processing speed and psychomotor efficiency. Digit Symbol Coding and Trail Making B were part of the battery for psychomotor speed and speed of

information processing with the addition of the Paced Auditory Serial Addition Test for speed of information processing. Brismar and colleagues (2007) argue that this is because these tests cover several different domains, however, this leads to cognitive domains that are highly interrelated without clear distinction for some variables.

There has also been an example of uncertainty in the conclusions because there are multiple processes involved in certain cognitive tasks that may better explain results. For example, Ryan et al., (2003) and Ryan (2005) suggest that psychomotor speed is the primary deficit in T1DM. However, the main test that Ryan (2005) has classified under the heading psychomotor speed is Grooved Pegboard. Ryan (2005) and others have found that individuals with T1DM do more poorly on Grooved Pegboard than control groups and show decline with age. Given that others have suggested that the main component of Grooved pegboard is motor performance, manual dexterity and strength (Lezak, 1995), this emphasizes the significant sex differences that occur in scores on this test. Due to smaller relative hand size, women do better than men. The difference in psychomotor speed may have more to do with motor than cognitive deficiencies in individuals with T1DM given the physical complications that can affect nerve functioning in this disease.

3.2. Cognitive Processes Identified in Research on Ageing

There are some areas of cognitive function that have been highlighted in research in cognitive ageing that will also be included in the cognitive battery given the goal to investigate evidence of early

cognitive ageing including two measures of memory - working memory, identified as one of the key cognitive processes in the ageing process (Park & Reuter-Lorenz, 2009) and episodic memory, an impairment common in diagnosis of mild cognitive impairment (Petersen, 2011).

3.2.1. Working Memory

Working memory is a "system typically involving attentional control and allowing the manipulation of information held in short-term storage" (Baddeley, 2007, p. 7), whereas short-term memory refers to the "immediate recall of small amounts of information" (Baddeley, 2007, p. 7). The model of working memory proposed by Baddeley and Logie (1999) includes a number of memory subsystems of the phonological loop, the visuo-spatial sketchpad, the central executive, and the episodic buffer. Working and short-term memory have been studied in research on healthy ageing. Tests include immediate recall of small amounts of auditory or visual information or complex recall with a component of further processing. The task used for this research, Digit Span (Wechsler, 1997), is a simple test of working memory that includes both storage and processing. Lezak (1995) based on evidence from neuropsychological patient performance on forward and backward Digit Span contends that backward Digit Span requires holding information and mentally rearranging, which is more effortful than the more passive task of forward Digit Span. In their work with children and adolescents, Gathercole, Pickering, Ambridge and Wearing (2004) classified forward Digit Span as a

verbal storage task and backward Digit Span as a storage and processing task or complex memory span task.

3.2.2. Episodic memory

Episodic memory involves memory for events from the past from a specific time and place (Tulving, 1972). There are a number of sub processes involved in episodic memory involved in the familiarity and recollection of past events (Purves et al., 2008). Typical tests that are used in the assessment of episodic memory include word list learning and story recall. These include either recall or recognition of learned information. These are classified as item memory tests that focus only on the content of the memory, with other tests that focus on the context, order, space or source in which the information was learned (Purves et al., 2008). This aspect of memory has not been related to T1DM, however is known to decline in healthy ageing (Salthouse, 2004).

3.3. Diabetes Health Variables and Cognitive Processes

The link between diabetes and specific deficits in cognitive processing has been studied by examining diabetes health variables that are proposed to underlie these cognitive changes related to the dysregulation of glucose levels in the body.

3.3.1. Repeated Severe Hypoglycaemia and Cognition

Findings from the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC), longitudinal studies of over 1000 patients

which followed a group with T1DM for 18 years, found that repeated episodes of severe hypoglycaemia were not associated with cognitive decline over the long-term (Jacobson et al., 2007). This finding has generally been replicated in some cross-sectional studies as well (Brismar et al., 2007) and in brain imaging research (Ferguson et al., 2003). Contradictory evidence has been found in a study of older adults, with severe hypoglycaemia performing worse on overall cognitive processing and information processing speed and who were more susceptible to cognitive decline (Van Duinkerken et al., 2011). The researchers suggest that older adults may be more vulnerable to the long-term effects of hypoglycaemia than younger adults. This variable may be of higher importance when exploring the reasons for cognitive function in older adult groups than in younger adult groups.

3.3.2. Chronic Hyperglycaemia and Cognition

There is conflicting evidence about the relationship of chronic hyperglycaemia, as measured by HbA1c percentage, and cognitive function. Various summary measures of high HbA1c have been used as a measure of chronic hyperglycaemia in studies of cognitive function and diabetes. Results of the DCCT/EDIC longitudinal study showed that patients with poor glycaemic control or mean HbA1c >8.8% (18 year mean value) were slower on measures of psychomotor efficiency and motor speed than those with better control or mean HbA1c<7.4% (Jacobson et al., 2007). Conversely, Brismar and colleagues (2007) using a more restricted measure of HbA1c (using on average of 5 years of values) found that this measure was only weakly correlated to

cognitive impairment and had no value as a predictor of cognitive function. Similarly, Zihl, Schaaf, and Zillmer (2010) using a single, current value of HbA1c did not find a difference in cognitive function between groups based on glycaemic control. One reason for these contradictory results may be the differences in the use of a long-term or short-term measure of HbA1c. Brismar and colleagues (2007) suggested that their value for mean HbA1c was not ideal, as it did not reflect lifetime glycaemic control or glucose instability. Since HbA1c levels vary within the same person for a variety of treatment and personal reasons, a restricted measurement may give a false or skewed value that does not best characterize glucose control over the long term. A mean HbA1c sampled over several years is needed to acquire a long-term measure of blood glucose control.

T1DM is often first diagnosed in childhood or adolescence. Given the brain is refining itself through adolescence and into the twenties (Casey, Tottenham, Liston, & Durston, 2005; Giedd, 2008), chronic hyperglycaemia during this period of continuing brain development may impact brain structure or function. Indeed, there is evidence of structural brain differences in children and adolescents compared with controls (Perantie et al. 2007), extending into adulthood (Musen et al., 2006). Brain imaging research has also provided evidence that implicates chronic hyperglycaemia in these structural differences. A study of children and adolescents (Perantie et al., 2007) showed hyperglycaemic exposure to be related to differences in gray and white matter density, years before the expected development of

microvascular complications. Musen and colleagues (2006) found evidence of reduced gray matter density in brain areas associated with memory (hippocampus, parahippocampal gyrus) language (superior temporal and angular gyrus) and attention (left posterior cingulate) for adults with a higher lifetime HbA1c average. Kodl and colleagues (2008) using Diffusion Tensor Imaging (DTI) analysis showed abnormalities in white matter structure for those with T1DM in comparison to controls in the posterior corona radiata and the optic radiation. Results indicated that chronic hyperglycaemia might have an independent effect on cognition. In contrast, when comparing groups that differed in glycaemic control or presence of microvascular disease (retinopathy), Weinger and colleagues (2008) showed that these groups did not differ in deep white matter or periventricular white matter lesions. The results of this study along with the results of the cognitive studies by Brismar and colleagues (2007) as well as Zihl and colleagues (2010) suggest that evidence on the influence of chronic hyperglycaemia on cognitive function is not conclusive.

3.3.3. Microvascular Complications and Cognition

Ryan (2005) found that complications including retinopathy, polyneuropathy and peripheral vascular disease were predictive of decline in psychomotor efficiency scores. Similarly, Ferguson and colleagues (2003) found that only those patients with T1DM who presented with background retinopathy showed differences in white matter and cognitive function. In a study assessing cognitive change after seven years for 103 middle age adults with childhood onset

diabetes, Ryan and colleagues (2003), found that changes in psychomotor efficiency over this period were strongly related to diabetic complications. A more recent study (Brismar et al., 2007) found that diabetes duration, age at diagnosis, and peripheral nerve conduction deficits (neuropathy) showed the strongest correlation with measures of psychomotor speed and visual – perception. Unlike the other studies, Brismar and colleagues (2007) did not find that retinopathy was predictive of cognitive decline. It is possible that the effects of retinopathy may have been masked by another variable correlated with retinopathy such as diabetes duration, which was identified as a primary predictor of cognitive deficit. The presence of retinopathy was correlated with many of the cognitive domains studied and was correlated with many of the other diabetes health variables studied.

Brain imaging studies show evidence of the importance of microvascular complications on cognition in T1DM. Ferguson and colleagues (2003) studied a group of individuals with T1DM with and without retinopathy under the age of 45. Those who developed retinopathy showed a significantly higher percentage of small punctuate white matter lesions than those without retinopathy in the basal ganglia. They suggested that this finding is consistent with the presence of enlarged perivascular spaces attributed to diabetic microangiopathy. They suggested that retinopathy is a marker of suboptimal control of diabetes and that cerebrovascular responsiveness in cognitive tasks may be compromised by retinopathy. There was no

decline in cognitive performance related to the presence of lesions, however the retinopathy group showed weaker cognitive performance on processing speed, attention and concentration, and fluid intelligence. They suggest cognitive differences stem from vascular cause and that impaired cerebrovascular responsiveness may be responsible for differences in cognitive functioning. Musen and colleagues (2006) associated the structural brain changes that they found to be related to hyperglycaemia exposure (a score combining median HbA1c and diabetes duration) as evidence for early microvascular damage. They suggest that changes in microvasculature due to retinopathy decreases vasoreactivity and blood flow, which causes deficits in cognitive function in T1DM.

Using functional Magnetic Resonance Imaging (fMRI) Wessels and colleagues (2006) showed a pattern of altered brain activation for individuals with T1DM and retinopathy on a working memory task (n-back) during induced hypoglycemia. The researchers found that there was no significant difference in task performance and reaction time between the groups with and without retinopathy. When comparing performance on the hard and easy version of the task during hypoglycaemia, the group with retinopathy showed greater activation (left occipital lobe) and no deactivation. The group without retinopathy showed deactivation in the anterior and posterior cingulate gyrus and left medial frontal gyrus. The group with retinopathy also showed increased activation during normal glycaemic values (euglycaemia) in the superior frontal gyrus. As well, the group with retinopathy showed

less deactivation when in hypoglycaemia compared with euglycaemia in the left anterior cingulate, right orbital frontal gyrus, and left parietal lobe. Finally there was an interaction with less deactivation in the right orbital frontal gyrus and left anterior cingulate cortex (ACC) in the group with retinopathy during hypoglycaemia. These two areas are part of the default mode network, which is active in rest and shows deactivation in cognitive tasks. They note that some proposed roles for the ACC including turning intentions into actions, willed control of behaviour and suppression of inappropriate responses. They note that the orbitofrontal cortex is involved in voluntary goal-directed behaviour and executive function.

Another study used resting state analysis to compare resting state neural connectivity in those with and without microvascular disease (Van Duinkerken et al., 2011). The researchers used independent component analysis and compared differences between those with severe microvascular disease (proliferative retinopathy) and without microvascular disease (no retinopathy) and controls between the ages of 18 and 56. Those with microvascular disease showed decreased connectivity in a variety of networks including attention, working memory, auditory, language, motor and visual processes.

Hyperglycaemia or microvascular complications?

Individuals with T1DM may sustain chronically high blood glucose for years before the signs of microvascular complications are evident. Chronic hyperglycaemia does show evidence of effects that are

independent of microvascular complications. Results of research with children and young adults, well before the onset of microvascular complications, also suggest that chronic hyperglycaemia has an independent effect on cognitive functioning (Perantie et al., 2007) that can be dissociated from that of microvascular disease. With an ageing group of individuals with T1DM with long duration, most will be affected by retinopathy to some degree (Diabetes UK, 2010). Young groups with T1DM have relatively lower rates of microvascular disease than older groups with T1DM, with small group size for comparison. It is therefore important to include both measures of mean HbA1c and microvascular complications, primarily retinopathy, when evaluating predictors of cognitive function.

3.3.4. Insulin Action

Insulin action is an emerging area of study in T1DM literature. Brismar and his colleagues (2007) theorized that cognitive impairment occurs because of a loss of neuro-protective effects of insulin. Biessels, Staekenborg, Brunner, Brayne, and Scheltens (2006) suggest that hyperinsulinaemia and insulin resistance play a role in the development of Alzheimer pathology of amyloid plaques given the number of insulin receptors found in crucial brain areas such as the hippocampus and cortex. High insulin, related to increased risk of strokes, also affects amyloid metabolism by changes in brain of insulin and its receptor and formation of advanced glycation end-products implicated in both normal ageing and dementia. Study of an older

group with long diabetes duration may allow the opportunity to investigate the importance of insulin resistance to understanding cognitive decline in this group.

3.4. Psychological Factors and Diabetes Health

Although there are a number of possible physical links to the deficits in cognitive function there are also personal characteristics and psychological variables that influence glycaemic control, which could influence the relationship between T1DM and cognition and these diabetes health variables.

3.4.1. Self-Management

In a prospective study, Skinner and Hampson (2001) investigated the impact of personal models of diabetes on diabetes self-care. They suggest that a personal model of diabetes or a person's illness beliefs can predict self-care, well-being and glycaemic control affecting a person's behaviour and emotions and is influenced by past experiences. A change in perceived impact of diabetes was positively correlated with anxiety and change in perceived effectiveness of treatment was positively correlated with dietary self-care. Watkins and colleagues (2000) found that when perception of control and understanding increased, this led to better dietary behaviours, less social and personal burden and fewer negative feelings regarding the disease and a more positive attitude in general. Better self-management can lead to better health outcomes in diabetes by improving glycaemic control and limit

the onset and severity of microvascular complications that have been related to deficits in cognitive deficits.

3.4.2. Intelligence

It may also be that a person's level of intelligence influences blood glucose control with lower intelligence leading to poorer ability to manage diabetes control. Gottfredson & Deary (2004) found that intelligence quotient (IQ) scores in childhood predicted adult morbidity and mortality and they suggest that this may be influenced by better ability for self-care. Taylor, Frier, Gold, & Deary (2003) found that those with more years of education had a better understanding of their diabetes at 4 and 12 months after diagnosis. Those with better knowledge early on had lower HbA1c at 12 months after diagnosis and this knowledge accounted for 5% of variance in glycaemic control. Premorbid IQ measured using the NART accounted for 11% of the variance in knowledge of diabetes at 12 months. However, they believe that psychosocial factors are more strongly associated with subjective outcomes such as quality of life, than objective outcomes such as HbA1c. IQ is an important indicator of cognitive reserve and a protective factor in the cognitive ageing process (Stern, 2002).

3.4.3. Depression and Anxiety

People with diabetes experience a higher rate of depression than those without diabetes (Ciechanowski, Katon, Russo, & Hirsch, 2003; Eaton, 2002; Heckbert et al., 2010). One study indicates a prevalence rate for depression of more than twice that of age and sex matched

controls based on cut-off score on questionnaire (Gendelman et al., 2009) and an increase in depression and anxiety symptoms overall (Collins, Corcorant, & Perry, 2009). A review of literature found that 40% of participants in clinic studies had elevated anxiety levels with 14% having Generalized Anxiety Disorder (Grigsby, Anderson, Feedland, Clouse, & Lustman, 2002). In a clinic setting, more than a quarter of patients with T1DM (age 18-80) indicate levels of anxiety and/or depression within a moderate to severe range using the Hospital Anxiety and Depression Scale (HADS; Lloyd, Dyert, & Barnett, 2000) with anxiety symptoms most prevalent at these levels. However, they found that the older adults (>33years of age) in the T1DM group exclusively reported moderate to severe symptoms of depression. In larger clinic study (n=259) of people between the ages of 16 and 60 with T1DM (Shaban et al., 2009) using the HADS, the mean anxiety rating was slightly higher than the mean depression. In comparison, values obtained for a normative non-clinic sample in the UK indicated that 12.6% showed moderate to severe levels of anxiety and 3.6 % moderate to severe depression (Crawford, Henry, Crombie, & Taylor, 2001). According to conclusions of a systematic review of the literature, the prevalence for depression, particularly in T1DM, has not been established due to limited number of well-designed studies and focus on symptom cut-off scores in self-report questionnaire (Barnard, Skinner & Peveler, 2006).

Van Tilburg and colleagues (2001) found that depressed mood was significantly related with sub-optimal glycaemic control in T1DM and

may be related to differences in self-care of diabetes. Anxiety has also been related to processing efficiency for control of inhibiting and switching attention (Derakshan & Eysenck, 2009). Results of a meta-analysis suggests that there may be a reciprocal relationship with poor glycaemic control leading to depressed mood and depressed mood influencing glycaemic control (Lustman et al., 2000). However, there is evidence that improvement in depression scores does not lead to better glycaemic control over time (Georgiades et al., 2007). Lloyd and colleagues (2000) found that those with retinopathy reported moderate to severe levels of anxiety more often than those with no retinopathy and those with neuropathy were more likely to report depression. They found that all those with T1DM and moderate to severe depression had poor glycaemic control. Given the higher incidence and link with poorer glycaemic control and microvascular complications, anxiety and depression are important considerations in the link between diabetes health variables and cognition.

3.5. Summary

There have been a few key areas of cognitive processing deficit identified in studies of younger adults with T1DM. These have included processing speed, executive function (cognitive flexibility) and both general and fluid intelligence. Other cognitive processes have been highlighted in ageing research including working memory and immediate and delayed episodic memory. Tasks that sample these cognitive processes will be used in the thesis studies. The cognitive processes identified are included in the current study reported in

Chapter 5. Evaluation of the incidence of MCI in the study group reported in Chapter 6 is based on participant performance across these cognitive processes.

Measures of blood glucose control and diabetes complications have been linked to cognitive functioning in T1DM. Some contradictory results may be due to the differing measures of HbA1c (long-term mean vs. single value or measure based on few years of data) and the low levels of microvascular complications present in younger age groups. There is evidence that measures such as repeated severe hypoglycaemia may have more importance in an ageing group though it has been dismissed as a significant factor in younger groups with T1DM. The influence of insulin resistance has not been studied in younger T1DM groups, but this factor is also more prevalent and may have more importance in an ageing group. These diabetes health variables will be used as predictors in the cognitive study reported in Chapter 5, and the study of the incidence and predictors of MCI reported in Chapter 6, in the study group. The psychological characteristics highlighted here that may have an added influence on diabetes control, complications and cognitive function are highlighted in Chapter 7.

Chapter 4
METHODOLOGY

This chapter provides information about the common methodology pertaining to all participants throughout the studies described in this thesis.

4.1. Participants

4.1.1. Recruitment

Participants were recruited between June 2009 and March 2011 from secondary care facilities hosting regular diabetes clinics within the Tayside region of Scotland. Clinics included those operating at Ninewells Hospital in Dundee, the Perth Royal Infirmary, and the Arbroath Royal Infirmary. Potential participants with upcoming clinic appointments who met diabetes type, diabetes duration, and age criteria (see Table 4.1) were sent a research invitation letter from the Consultant supervising the research (Appendix A), an introductory letter (Appendix B), participant information sheet (Appendix C), and response card (Appendix D) to indicate agreement or disagreement to be contacted by the researcher for more information about the study. In addition, patients listed on the Scottish Diabetes Research Network (SDRN) Research Register, who had given agreement to be contacted for any diabetes study, were contacted directly by the researcher to ask if they would like to receive information about the study.

4.1.2. Inclusion and Exclusion Criteria

The researcher went through a brief inclusion/exclusion questionnaire with participants over the phone to determine eligibility to take part in the study (Appendix E). The inclusion and exclusion criteria are presented in Table 4.1.

Table 4.1 *Inclusion and Exclusion Criteria for Study 1*

Inclusion Criteria	**Exclusion Criteria**
• Age 45 and over • Diabetes duration of 10 years since diagnosis. • English-Speaker	Conditions or characteristics that would affect results of cognitive assessment including: • Diagnosed disease or injury affecting brain (stroke, brain injury, dementia, mild cognitive impairment confirmed through medical diagnosis) • Diagnosis of major psychiatric disorder (e.g. schizophrenia, major depression or anxiety disorder) • self-identified or doctor-identified alcohol or drug use problem/addiction • visual impairment or hearing deficits • non-English speaker.

4.2. Sample Size Feasibility

To check the feasibility of the sample size, a query was conducted by the Managed Clinical Network (MCN) data facilitator using information from the Scottish Care Information – Diabetes Collaboration (SCI-DC) clinical management system (McAlpine, November 2008). The results of the query revealed that, in Tayside there were 625 individuals over 40 with a diabetes duration of 10 years or more and 331 over the age of 50. An age cut-off of 45 was chosen as optimal to focus on older patients as much as possible and maximize the number of potential participants for the study (see Table 4.2).

Table 4.2 *Tayside Patients with Type 1 diabetes Grouped by Average HbA1c*

	Age > 40		Age > 50	
HbA1c	Number	Percentage	Number	Percentage
</= 7	48	8	21	6
7.1 to 9	378	60	218	66
> 9	199	32	92	28
All	625	100	331	100

As this is a sample of convenience, ultimately the groups were divided based on actual mean HbA1c of the participants in tertiles to create groups that are similar in size for comparison. Assuming about half the individuals between 40 and 50 are 45 and over, there will be about 470 patients aged 45 and above. The goal was to recruit a sample of 150 or 32% of potential participants based on the results of the sample size feasibility and power analysis detailed below.

4.2.1. Participant Recruitment Statistics

In practice 451 potential participants were contacted and the final response decisions, numbers, and percentages are detailed in Table 4.3. The targeted recruitment level of 150 was not achieved due to exhausting the clinic lists and research register for the three Tayside clinic sites. Although application was made to add another clinic site outside of the Tayside region (St. Andrews in Fife) to increase patient recruitment, approval came too late (March 2011) to allow recruitment at this site.

Out of the 451 research invitations sent, just over 27% expressed a willingness to take part in the study. Of those who responded yes to the research invitation (n=124), over three quarters were included (n=94). One fifth of the group who said yes was excluded due to incorrect diagnosis, short duration of diabetes, visual or hearing impairments, or onset of hypoglycaemia during testing (Table 4.3). The majority was excluded due to the existence of a medical condition that may affect cognition including stroke, transient ischemic attack (TIA), epilepsy, or encephalopathy or diagnosed anxiety or depression. Those with limited acute or past use of anti-depressant medications and no self-identified concerns with depression were permitted to participate. Only 4 people who originally consented withdrew themselves from the study. Of these, only one person asked to discontinue after the start of testing. Of the other three, one did not show up for the appointment, and two cancelled their appointments.

Table 4.3 *Participant Recruitment Statistics*

	Total (n)	Percent of Total (%)
Participant Invitations	451	100
No Response	244	54.1
Response Total	207	45.9
No	84	18.6
Yes	124	27.5
Included	94	75.8
Excluded	30	24.2
Type 2 diabetes	1	4
Duration <10 years	2	8
Medical condition	10	40
Anxiety/Depression	7	28
Inconvenient to attend	2	8
Hypo during testing	3	11.5
Uncorrected vision	1	4
Elected to Withdraw	4	3.25

There was no specific information available on the exclusions regarding diabetes health as only limited patient information was accessed to contact potential participants. Those who withdrew from the study did not systematically differ from those who were included in the study. The majority were male (n=18), they had a wide age range (48 – 74 years) and from short to long duration of diabetes (7 – 52 years). The information available is provided in Table 4.4

Table 4.4 *Excluded Participants*

Total Number	Gender (Number)		Age Mean (SD) Range	Duration of Diabetes (SD) Range
	Male	Female		
30	18	12	57.8 (8.27) 48 - 74	29.1 (14.75) 7-52

4.3. Independent Variables:

4.3.1. General and Diabetes Health Variables

The following general and diabetes health variables were collected along with demographic information (age, gender, education) for all participants through medical records including SCI-DC, and questionnaires completed before the cognitive testing session (see Appendix I & Appendix J). Each measure of diabetes health, general health variables and health promoting habits along with the method to obtain or derive the variable is listed in Table 4.5. More detailed information about the measures of diabetes control and complications is provided below.

Table 4.5 *Participant Health Information Collected for Study 1*

Information	Derived Variable
1. Age at Diagnosis	Age in years when diagnosed
2. Duration of Diagnosis	Years since first diagnosis
3. Waist/Hip Ratio	Calculated from waist/hip measurements taken at testing session
4. Body Mass Index	Value on record at time of study
5. Blood Pressure	a. Systolic BP at time of study
	b. Diastolic BP at time of study
6. Cholesterol	a. Total Cholesterol at time of study
	b. HDL Cholesterol at time of study
	c. Triglycerides
7. Exercise	a. Rate Less/Same/More than age peers
	b. Rate of Perceived Exertion (RPE) - self-rating on 10 point Likert-type scale from Low to Strong
8. Cognitive Activity	a. Rate Less/Same/More than age peers
9. HbA1c	a. Frequency weighted mean HbA1c
	b. Current HbA1c – HbA1c at testing
	c. Recent HbA1c–5 year mean HbA1c
	d. HbA1c SD – HbA1c Standard Deviation based on mean HbA1c

Table 4.5 (cont.)

Information	Derived Variable
10. Retinopathy	Rating based on Scottish Diabetic Retinopathy Grading Scheme of retinopathy and maculopathy
11. Neuropathy	Rating based on foot risk score
12. Nephropathy	Rating based on albuminuria level
13. Microvascular Total	Combination of retinopathy, maculopathy, neuropathy and nephropathy ratings
14. Hypoglycaemic Events	Average hypos per year determined by number of events/duration of diabetes
15. Insulin Resistance	Estimated Glucose Disposal Rate (eGDR)

1. Age at Diagnosis

Self-report of the participant's age at first diagnosis

2. Duration of Diagnosis

Participant age at diagnosis subtracted from current age

3. Waist/Hip ratio

The researcher took participant waist and hip measurements at the testing session. The waist/hip ratio was calculated from these values.

4. Body Mass Index (BMI)

BMI is calculated at the participant's clinic appointment and reported through SCI-DC.

5. Blood Pressure (BP)

Systolic BP and Diastolic BP values are taken by the nurse at the participant's clinic appointment and reported through SCI-DC.

6. Cholesterol

Values for High-Density Lipoprotein (HDL), Total Cholesterol and Triglycerides taken at the participant's clinic appointment and reported through SCI-DC

7. Exercise

Level of physical activity: A global rating of daily physical activity based on Sternfeld, Cauley, Harlow, Liu, & Lee (2000) asks participants to compare their own physical activity to that of their age peers and rate their level of physical activity as "much less", "less", "the same as", "more" or "much more" than others of their age.

Rate of Perceived Exertion (RPE): Self-rating of usual exercise intensity using the 10-point Rate of Perceived Exertion (RPE) scale (American Council on Exercise, 2001).

8. Cognitive Activity

A global rating of daily cognitive activity, using the same rating scale for the global rating of physical activity described above, will be used to rate participant engagement in cognitive activities.

9. Measures of HbA1c

Frequency weighted mean HbA1c: Based on 10 years or more of HbA1c values with a range from 7 to 20 years of values ($\bar{x}$=16.3, SD=4). Although all participants were diagnosed with diabetes for at least 10 years, for a small number of participants (n=4), this mean is

based on 7 to 9 years of values due to missing records from previous secondary care clinics within England. The researcher requested past records from clinics in England; however, this was not always successful. One participant had HbA1c scores for only 5 years. This participant was excluded from analyses using weighted mean HbA1c only.

The method of determining frequency weighted HbA1c and frequency weighted standard deviation of HbA1c was developed in consultation with Dr. Christie Marr (May 2010), who at the time was Head of the Mathematics Support Centre at the University of St Andrews. It was decided that a frequency weighted mean based on the number of days between readings would be most accurate for this data set as there were not always an even number of days between readings (e.g., 2 HbA1c readings for 2005 could be within 1 month of each other and for 2007 could be within 6 months of one another). It was assumed that HbA1c values taken closer in time would be more similar and therefore should have lower weighting in the overall mean than those readings taken further apart in time. Given that the SCI-DC record includes entries from both secondary and primary care facilities, HbA1c tests could be either more frequent for some participants, or the same data may have been entered more than once, on different days (McAlpine, October 21, 2009).

Each HbA1c value was multiplied by the value for days between readings. These values were then summed and divided by the sum of days between readings shown in Equation 4.1. Step by step details of

the method for deriving frequency weighted HbA1c can be found in Appendix K.

Equation 4.1

$$\text{Frequency Weighted Mean HbA1c} = \frac{\sum x_i w_i}{\sum w_i}$$

x= HbA1c Value ; w= Number of days between readings

Frequency Weighted HbA1c SD: These values used to calculate mean HbA1c were also used to determine a frequency weighted standard deviation of HbA1c scores shown in Equation 4.2.

Equation 4.2

$$\text{Frequency Weighted HbA1c SD} = \frac{\sum x_i^2 w_i}{\sum w_i / n}$$

x= HbA1c Value ; w= Number of days between readings; n=number of readings

Current HbA1c: HbA1c value at time of study participation

Recent HbA1c: Frequency weighted mean HbA1c over past 5 years

10. Retinopathy

Retinopathy ratings were taken from the SCI-DC or paper medical record based on the Scottish Diabetic Retinopathy Grading (SDRG) Scheme 2007 v1.1 (Scottish Diabetic Retinopathy Screening Collaborative, 2007). The SDRG is the hierarchical grading system used to assess severity of retinopathy. This results in 5 levels of

retinopathy severity from lowest - 0 (no retinopathy) to highest - 4 (proliferative retinopathy). Retinopathy grading is subject to improvement (i.e., decrease from higher to lower severity) if participants received laser treatment. Retinopathy was graded as the highest rating on record for either eye. Given the small number of participants with no retinopathy in the sample (n=3) this group was combined with the mild retinopathy group in analyses. In some analyses the Referable and Proliferative groups were combined as a High Severity Retinopathy group given that all are referred for ophthalmology and/or laser treatment. Laser treated retinopathy or maculopathy was included in the proliferative retinopathy category. as indicated in Table 4.6.

Table 4.6 *Retinopathy Coding and Frequency in Study 1 Sample*

Retinopathy Severity	Code	Frequency in Total Sample
No Retinopathy	0	3
Mild Background Diabetic Retinopathy	1	15
Observable Background Diabetic Retinopathy or Observable Maculopathy	2	22
Referable Background Diabetic Retinopathy or Referable Maculopathy	3	21
Proliferative Diabetic Retinopathy or Laser Treated Retinopathy/Maculopathy	4	33

11. Neuropathy

The grading for neuropathy was based on the foot risk score provided in SCI-DC. The most current risk score was used. Frequency analysis indicated that 75% of the study 1 participants were considered to be in the lowest risk category, 15% moderate risk and 10% high risk.

12. Nephropathy

Nephropathy was rated based on albuminuria level. Most participants had normal albuminuria levels (87%) with an even split between those with microalbuminuria and macro or clinical albuminuria (13%). Given the limited numbers with elevated neuropathy and nephropathy risk in this sample, these variables were not considered independently in analysis, but combined with retinopathy severity to get a microvascular total score.

13. Microvascular Total

A combined rating of microvascular burden derived by adding retinopathy, neuropathy and nephropathy ratings together weighted by the number of rating levels within each variable, shown in Equation 4.3

Equation 4.3

Microvascular Total =

Retinopathy Level/5 + Neuropathy Level/3 + Nephropathy Level/3

14. Hypoglycaemic Events

Participants were asked to rate how frequently they had experienced hypoglycaemic events (requiring assistance or hospitalization). This was estimated by questions on the Diabetes

Questionnaire (Appendix I) based on a method used by Brismar and colleagues (2007). Participants gave the absolute number of these events or an estimate of the number they typically experience per year. The number of hypoglycaemic events was divided by duration of diabetes to get an estimate of hypoglycaemia exposure based on duration, "average hypos per year". Eighty-eight percent of the sample had values indicating they experience an average of less than 1 hypo per year. The average hypos per year value ranged from 0 to 12. Given the wide variation and non-normal distribution in average hypos per year, these values were coded for severity (0 = never; 1=less than 0.06/year; 2= more than 0.06 per year) to make similar sized groups for comparison.

15. Insulin Resistance

Insulin resistance can be estimated through the calculation of estimated glucose disposal rate (eGDR). Olson and colleagues (2002) provide the equation to calculate eGDR based on their earlier work (Williams, Erbey, Becker, Arslanian, & Orchard, 2000) shown in Equation 4.4. There is an inverse relationship between eGDR and insulin resistance with lower eGDR scores related to higher levels of insulin resistance (Williams et al., 2000). Therefore, higher eGDR scores relate to better diabetes health.

Equation 4.4

$$eGDR=24.31-(12.22*\text{Waist-Hip Ratio}) -(3.29\ \text{Hypertension})-(0.57*\text{HbA1c})$$

4.4. Dependent Variables: Cognitive Battery

Each participant completed the following cognitive battery administered by the researcher. These were used as predictors and/or covariates in the analyses. Table 4.7 displays the tests in the cognitive battery listed in order of administration and the average time to complete each test.

Table 4.7 *Cognitive Battery*

Cognitive Tests in Administration Order	**Average Administration Time in Minutes**
1. National Adult Reading Test	3
2. Adult Memory and Information Processing Battery Story Recall – Immediate	5
3. Raven's Standard Progressive Matrices	25
4. Adult Memory and Information Processing Battery Story Recall – Delayed	2
5. Symbol Digit Modalities Test – Written and Oral	5
6. Digit Span Forward and Backward	5
7. Trail Making A & B	5
Total of 7 cognitive tests	50

The tests used for the cognitive battery in relation to the cognitive domain are presented in Table 4.8.

The cognitive domains were chosen based on the domains with the largest effect sizes in the meta-analysis of T1DM and cognition research (Brands et al., 2005) including processing speed, executive

function (i.e., set shifting) and indices of general intelligence. Tests of working memory and episodic memory were also included as these processes are important in cognitive ageing research (Hedden & Gabrieli, 2004). The test(s) chosen for each domain are discussed in turn. A sample of the type of material presented for all the cognitive tests with a visual presentation format is provided in Appendix L. Scoring details for raw score to standard score conversion for each cognitive test are provided in Appendix M.

1. Processing Speed : Symbol Digit Modalities Test

The Symbol Digit Modalities Test (SDMT; Smith, 1982) is a test of processing speed and more specifically meets Salthouse's (2000) criteria for a test of perceptual speed. It is a simple paper-and-pencil cognitive task with a time limit. At the top of the page there is a key that pairs a symbol with each number from one to nine. At the bottom of the page are several rows of these symbols with the numbers missing (Appendix L). Participants are asked to fill in the correct number for each symbol for as many symbols as possible within a 90 second time limit. Using what should be a well-practiced motor skill, writing of single digit numbers, minimizes the motor component of this task. This task draws on processes including attention, visual scanning and motor speed (Sheridan et al., 2006). This test was administered in both a written and oral format as physical motor speed may influence the deficits that T1DM groups have on this type of task. Scoring was based on the number correct within 90 seconds. This test was presented and

scored according to the standard administration procedures and norms provided (Smith, 1982).

Table 4.8 *Cognitive Tests Used Within Selected Cognitive Domain*

Cognitive Domain	**Test**
Processing Speed: Perceptual Speed	Symbol Digit Modalities Written & Oral ; Trail Making A
Executive Function: Set Shifting	Trail Making B
Crystalized (Premorbid) IQ	National Adult Reading Test
Fluid Reasoning	Ravens Standard Progressive Matrices
Estimated Lifetime Cognitive Change (ELCC)	NART-Ravens Regression
Age-Adjusted Lifetime Cognitive Change (A-ELCC)	Age-ELCC Regression
Episodic Memory	Adult Memory and Information Processing Battery Story Recall Immediate & Delayed
Short-term/Working Memory	WAIS-III Digit Span

2. Processing Speed and Set Shifting: Trail Making Test A & B

The Trail Making Test (TMT; Army Individual Test Battery, 1944) is widely used in neuropsychological testing. The TMT A, is a

paper-and-pencil task in which participants are asked to draw a line to connect numbers starting at 1 in consecutive order as quickly as possible (Appendix L). This task meets Salthouse's (2000) definition of a test of perceptual speed given the low cognitive complexity and timed response. On the TMT-B, participants are presented with another sheet of paper including both numbers and letters. They are asked to alternate between making a trail connecting numbers (starting from 1) and letters (starting from A) as quickly as possible (Appendix L). This task involves an executive component as participants must alternate or shift between two tasks. Scores will include the amount of time in seconds required to complete each task. The TMT A & B were administered and scored using the guidelines and normative data developed by Spreen, and Strauss (1998).

3. Premorbid IQ: National Adult Reading Test (2nd edition).

The National Adult Reading Test-2nd edition (NART; Nelson & Willison, 1991) is a measure of vocabulary knowledge that is resistant to neurological impairment processes and has strong correlation with standard measures of verbal IQ (Lezak, 1995) and provides an estimate of premorbid IQ. The NART is therefore a measure of crystallized intelligence and scholarly knowledge (Brands et al., 2005). Participants are asked to read a list of progressively difficult and phonetically irregular English words. The scores include the total number of errors (for conversion to Full Scale IQ equivalent) and the total number correct out of 50 (for the calculation or the Estimate of Lifetime

Cognitive Change). The NART was administered according to standard procedures (Nelson & Willison, 1991).

4. Fluid Reasoning: Raven's Standard Progressive Matrices

For the Raven's Standard Progressive Matrices (Raven's SPM; Raven, Raven, & Court, 2003), the participant is asked to choose from a group of pictures to best complete a missing piece of a pattern or matrix (Appendix L). This test was administered following the standard administration procedures (Raven et al., 2003) with a time limit of 20 minutes for calculation of the Estimate of Lifetime Cognitive Change score (Deary et al., 2004). The score is the number of items correct within the time limit. There were no norms available for the 20-minute administration.

5. Estimate of Lifetime Cognitive Change

To get an estimate of change in cognitive functioning across time without having a previous IQ score, Deary et al., (2004) studied the Scottish Mental Survey cohort of 1932 to establish the validity of an Estimate of Lifetime Cognitive Change (ELCC). The ELCC score is the standardized residual score (z score) that is calculated using linear regression. Using the regression-based difference between raw scores on the NART and Raven's (20min time limit) to adjust current ability (Raven's) with an estimate of prior ability (NART number correct). The standardized residual difference scores (z scores) provide an estimate of cognitive change with a positive score indicating a relative

positive change in estimated cognitive function and a negative score indicating a relative decline in cognitive function. Deary and his colleagues (2004) found a strong relationship between IQ scores at age 11 and IQ scores at age 77 and 78, a measure of actual cognitive change in the 1932 cohort. Pearson correlation revealed that the ELCC score had a strong negative relationship with age in the sample (r=-.49, p<.01, one-tailed) . Given the wide age range of participants, a further regression analysis was used to adjust the ELCC score using age as a dependent variable. Pearson correlation revealed that the resulting age-adjusted estimate of lifetime cognitive change (A-ELCC) score was not significantly correlated with age (r=.00, p = .50, one-tailed).

6. Episodic Memory: AMIPB: Story Recall Immediate and Delayed

The Story Recall Immediate (SRI) and Story Recall Delayed (SRD) tests of the Adult Memory and Information Processing Battery (Coughlan & Hollows, 1985) were used to assess episodic memory. On this tests participants are asked to recall as much of a story as possible, both immediately and after a 30 minute delay. The score is based on the number of ideas correctly recalled. Each idea could receive a score between 0 and 2, depending on the accuracy of the recall (0=missed/incorrect; 1=partially correct; 2=correct), for a maximum of 58 points. This test was administered and scored following standardized procedures and using norms provided (Coughlan & Hollows, 1985).

7. Short-Term / Working Memory :Digit Span

The Digit Span task is a simple test from the Wechsler Adult Intelligence Scale (Wechsler, 1997). Participants are asked to repeat small strings of numbers both forwards and backwards. Digit Span Forwards (DSF) is a measure of span of attention and verbal short-term memory and digit span backwards (DSB) a measure of simple working memory including both storage and processing. The score is based on the number of items correct for both DSF and DSB out of 30. The test is administered and scored using standard test procedures and norms (Wechsler, 1997).

4.4.1. Procedure

Participants completed a series of short questionnaires and a cognitive assessment battery. For the majority of participants, this session took place before or after their scheduled clinic appointment and for others it was scheduled on a separate day when convenient for the patient. The questionnaires were given to the participants while they waited for their clinic appointment and took 10 to 15 minutes to complete. Participants completed the cognitive assessment battery with the researcher, a Registered Educational Psychologist (Canada). Before the cognitive assessment started, participants were asked to check their blood glucose. If below a value of 4 mmol/litre, the participant had a glucose drink (lucozade), provided by the Diabetes Centre as a standard protocol for treating hypoglycaemia. Testing started after further blood glucose check shows a level of blood glucose above 4 mmol/litre. Despite this check, it was discovered during the session

that some participants took on hypoglycaemia after the start of the test. These individuals were provided a glucose drink and were tested to ensure blood glucose was normal, however as noted above their results were excluded from the analysis. The blood glucose level at the time of testing was recorded for each participant. The participants' responses to some tests were video-recorded for scoring purposes. For the majority of participants it took approximately 50 minutes to complete the test battery.

4.5. Statistics

4.5.1. Within-Group Comparison

To examine the impact of diabetes health variables on cognitive function the participants were divided into groups based on the diabetes health variables (HbA1c level, retinopathy severity) and presence of MCI. A healthy control group was not recruited as it has already been established that there is a difference in specific areas of cognitive function between groups with and without diabetes. Instead the study was designed to get a better understanding of the possible reasons for this difference. Further confirmation of a difference between groups with T1DM and healthy controls would not provide this information.

4.5.2. Power analysis

Analysis of Variance

A power calculation was completed using the R statistical

program (http://www.R-project.org) for one-way analysis of variance. The effect size entered was 0.3, the lowest effect size for cognitive domains in a meta-analysis of cognitive studies on T1DM in comparison to controls (Brands et al., 2005). A conservative estimate was used to cover all cognitive domains in the proposed research. For a power of .8, with a significance level of .05, the sample size was estimated to be a minimum of 37 for each of three groups in the analysis or n=111. There were higher effect sizes reported for psychomotor efficiency (~0.6), cognitive flexibility (~0.5), fluid intelligence (~0.5), crystallized intelligence (~0.8); lower effect sizes were reported for working memory (~0.1), immediate memory (~0.1), and delayed memory (~0.2). Smaller size groups would be required for sufficient power for measures of intelligence, processing speed and executive function (cognitive flexibility) ranging from 7 to 14 participants for each of 3 groups. A sample size of over 300 per group is required for sufficient power at an effect size of only 0.1 and over 80 for an effect size of 0.2. These domains are included given their importance in ageing research and were included for exploratory purposes given the current study sample is older than the typical samples found in T1DM studies (Brands et al., 2005).

Multiple Regression

Power analysis for multiple regression was completed using the pwr package (Champely, 2009) for the R statistical program (http://www.R-project.org). The effect size for this calculation (f2) was calculated using a known R^2 value ($f2 = R^2 / 1- R^2$). There were no

estimations of R^2 reported in the T1 literature for groups similar to the age range for this study. The R^2 values used in the power calculations were taken from a regression analysis by Brismar and colleagues (2007) with an age range of 22 to 55 years of age. Table 4.9 provides the results of power calculations using the R^2 values from the Brismar (2007) study for cognitive domains which will also be assessed in the current study using a power of .8 and significance level of .05 for both the target sample size of 150 and the actual sample size of 94. Given the actual sample size and low effect sizes for some cognitive domains, only measures of processing speed and general intelligence (premorbid IQ and fluid reasoning) were used in multiple regression analysis.

Table 4.9 *Number of Predictor Variables for Multiple Regression Analysis*

Cognitive Domain	R^2 value	Effect Size (f2)	Target Sample Size n=150	Actual Sample Size n=94
			Number of Predictors	
Perceptual Speed	0.156	0.185	51	13
General Intelligence	0.145	0.17	39	10
Memory	0.11	0.124	15	4
Executive	0.074	0.080	4	0
Working Memory	0.072	0.078	4	0

4.6. Transformation of variables for normal distribution

Due to non-normal distribution of some variables, some transformations and/or minimization of outlier values were required. A number of methods were used to normalize the distribution for each variable to be entered into the general linear model analysis techniques based on methods described by Field (2005) including minimizing outliers based on the mean and standard deviation of the variable and using log and square root transformations. The details of required transformations are provided in Appendix N and when used indicated within each study chapter when necessary.

4.7. Summary

This chapter provided an introduction of the methodology common to the studies contained in this thesis. All or a sub-group of these participants took part in the studies that follow. The diabetes and cognitive variables are highlighted throughout these studies. General health variables and health habits are examined within the cognitive study in Chapter 5 and the MCI study in Chapter 6. Psychological variables are the focus of Chapter 7.

Chapter 5
Predictors of Cognitive Function In Middle and Older Aged Adults With Type 1 Diabetes

5.1. Introduction

Individuals with T1DM are encouraged to maintain strict glyceamic control to prevent onset of microvascular and macrovascular complications. Chronic hyperglycaemia and its related complications have been identified as a potential link to relative cognitive deficits in groups with T1DM (Wessels, Scheltens, Barkhof, & Heine, 2008). Many previous studies do not have access to long-term information about glycaemic control, exclude participants with microvascular disease (a marker of poor glycaemic control), or focus only on young adults.

The purpose of this research study is to evaluate the relationship between glycaemic control (as measured by HbA1c), related diabetes complications, general health, and cognitive processing in a middle aged and older group with T1DM. This research study aims to determine whether signs of early cognitive ageing may be found in groups that have poorer diabetes health or general health and to identify the strongest diabetes health predictor of cognitive function. The strongest predictor was used as a way to determine comparison groups in the functional MRI study, as it was presumed that this factor would also be most likely to have an impact on brain functioning.

The first part of the study will compare individuals with T1DM, who have varying levels of long-term glycaemic control, directly on

tasks representing a spectrum of cognitive processes that have been highlighted by both the T1DM and cognitive ageing research. The predictive value and relative importance of long-term glycaemic control on cognitive performance was evaluated along with the relative contribution of other diabetes complications and general health factors known or presumed to impact cognitive function. This study included a group of individuals with a higher mean age than is typically studied in T1DM (Brands et al., 2005) to maximize the potential for finding between-group cognitive differences, that may indicate signs of early cognitive ageing.

5.2. Study Questions

Question 1: Do individuals who differ on glycaemic control and other diabetes health variables show significantly different scores on measures of cognitive processes?

Question 2: Is cognitive function related to general health variables and health promoting habits?

Question 3: Which diabetes health variables have the strongest predictive value on cognitive function?

5.3. Ethics

A favourable ethical opinion was obtained (Appendix F) through the Tayside Committee on Medical Research Ethics A, an arm of the East of Scotland Research Ethics Service for the National Health Service (NHS). Approval to conduct the study on NHS Sites and with the assistance of NHS staff was sought through the NHS Research and

Development Office (Appendix G). Ethical approval was also sought and obtained through the University Teaching and Research Ethics Committee (UTREC) for the University of St. Andrews (Appendix H).

Access to past and present medical records, both paper and computerized files, was also required. As such, it was necessary to seek approval to allow access to these records through the NHS Tayside Caldicott Guardian who is the person responsible to protect the confidentiality of patient information. Caldicott Guardian approval was obtained as required. The study also had to be registered with NHS Tayside Diabetes Managed Clinical Network (MCN) and the Scottish Diabetes Research Network (SDRN) to acquire access rights to computerized patient records for participants through the clinical management system SCI-DC (Scottish Care Information – Diabetes Collaboration) and to access the SDRN Research Register to obtain patient contact information for patients who had already provided permission to contact for any diabetes study. Approval to access paper medical records was secured with the respective medical records departments for each secondary care facility.

5.4. Methods

The methods for the cognitive study are described in Chapter 4. Participants completed the diabetes health and well-being questionnaires and the cognitive battery. Diabetes and information about general health variables was collected from medical records as described.

5.5. Statistical Analysis

5.5.1. Correlation

Pearson correlation and Spearman's rho were used for the correlation analysis to identify demographic, diabetes health variables and general health variables important for further analysis. Diabetes health variables including mean HbA1c (and variants such as current/recent HbA1c and HbA1c standard deviation), diabetes burden (duration, age of onset), and diabetes complications (retinopathy, microvascular disease, severe hypoglycaemic, insulin resistance) were examined for their relationship with cognitive processing scores and the inter-correlation between these variables. The complete results of this analysis are presented in (Appendix O) with specific correlations of interest highlighted within this chapter. One-tailed significance values are used to ensure identification of all potential relationships of interest and variables to be controlled and included in further analysis.

5.5.2. Analysis of Variance

Participants were split into three similar sized groups based on tertile scores for frequency weighted mean HbA1c (Low ≤7.9%, Midrange 8.0-8.8%, High ≥8.9%). Between-group differences were investigated using general linear model analysis of variance (ANOVA) or analysis of covariance (ANCOVA) in all cognitive domains and on the age-adjusted estimate of lifetime cognitive change (A-ELCC) to examine main effects of mean HbA1c group and retinopathy severity. A factorial ANOVA was used to further explore the relationship between

mean HbA1c, retinopathy severity and cognitive function in areas in which a significant effect of either mean HbA1c or retinopathy severity was found. Planned comparisons were completed irrespective of the significance of the *F*-test given that these comparisons are hypothesis driven based on the results of previous research and the number of planned comparisons (2) is one less than the number of groups (Karpinski, 2011). Information from this analysis was used to identify potential diabetes health variables to use as predictors for multiple regression analysis.

5.5.3. Multiple Regression

Mean HbA1c was entered into a multiple regression analysis with other diabetes factors chosen on basis of importance in previous regression analyses (e.g., duration of diabetes, microvascular diseases, severe hypoglycaemic events). The dependent variables were scores on age-adjusted cognitive change and cognitive tasks. This analysis was used to determine the strongest predictor of cognitive processing scores.

5.6. Results

Participant Demographics and Relation to Diabetes Health

The demographic characteristics of the participants are presented in Table 5.1. Spearman's rho was used to investigate the relationship between demographic variables and diabetes health variables with correlations of interest highlighted in the text. This was used to identify potential demographic variables to control or include in

further analyses. The complete correlation table is provided in Appendix O for reference.

Age

Older Age is positively correlated with longer duration of diagnosis (r_s=.381, p=.000), higher age of onset (r_s=.271, p=.004), higher severity of retinopathy (r_s=.276, p=.004), and greater total microvascular disease (r_s=.310, p=.001). Age is also positively correlated to NART-IQ (r_s=.222, p=.016). When controlling for NART-IQ in partial correlation the relationship remains significant between age and higher severity of retinopathy (pr_s=.294, p=.002) and greater total microvascular disease (pr_s=.371, p=.000). It will be important to control for age to when evaluating these values as predictors of cognitive function. Participant age was controlled in the analysis of cognitive function by using z-scores based on age norms.

Table 5.1 *Participant Demographic and Diabetes Characteristics*

Variable	Range	Mean	Std. Error	Std. Deviation
Age (years)	45.0 - 80.7	58.7	.10	8.79
Education (years)	9 – 25	14.2	.37	3.55
Premorbid Intelligence (NART IQ)	94 – 126	114.2	.71	6.83
Diabetes Duration (years)	11.1 - 67.8	31.9	1.3	12.0
Age of Onset (years)	4.6 - 59.1	26.8	1.2	11.2
*Weighted Mean HbA1c (%)	6 – 12	8.4	.10	.933
Weighted HbA1c Std. Deviation (%)	.36 – 2.7	.94	.04	.36

*n=93

Gender

Female gender was associated with higher eGDR (r_s=.571, p=.000), which is indicative of lower insulin resistance. Female gender is also associated with lower waist-hip ratio values (r_s=-.691, p=.000) and lower hypertension (r_s=-.243, p=.009) which are the main factors used to calculate eGDR and suggests better overall general health in this group. Gender was included in multiple regression as it has a relationship with general health variables in the study.

Education

Higher years of education is related to lower current HbA1c value (r_s=-.223, p=.02), lower recent HbA1c value (r_s=-.191, p=.03), and lower total microvascular disease (r_s=-.227, p=.014). However, education also has a positive relationship with NART-IQ (r_s=.488, p=.000). Results of partial Spearman's rho correlation indicate that the relationship between education and HbA1c values becomes insignificant when controlling for IQ for both current HbA1c values (pr_s=-.126, p=.114) and recent HbA1c (pr_s=-.127, p=.113). Age has a positive relationship with microvascular disease (r_s=.310, p<.01). The relationship between education and microvascular disease remains when controlling for age (pr_s=-.213, p=.020). NART-IQ is included as a variable when evaluating predictors of cognitive function, given its relationship with education.

Premorbid IQ

Higher premorbid IQ (NART-IQ) is related to lower current HbA1c (r_s=-.237, p=.011), however this relationship does not remain when controlling for participant education (pr_s=-.150, p=.075). Higher NART-IQ is also related to higher age of onset (r_s=.190, p=.03), however this relationship does not remain when controlling for age (pr_s=.138, p=.094). Higher pre-morbid IQ is related to lower microvascular disease (r_s=-.199, p=.03), and this relationship is strengthened when controlling for participant age (pr_s=-.289, p=.002). Higher NART-IQ is also related to lower long-term variability in HbA1c (r_s=-.209, p=.02). This relationship remains when controlling

for participant age (pr_s=-.197, p=.029). NART-IQ is included as a predictor in the multiple regression analysis.

5.6.1. Glucose Control and Cognitive Function

Question 1: Do individuals who differ on glycaemic control and other diabetes health variables show significantly different scores on measures of cognitive processes?

Glycaemic Control

Mean HbA1c. For comparison of the effect of glucose control on cognitive function, three groups were formed based on based on tertile cut-off points for long-term (≥ 10 years) frequency weighted mean HbA1c (Low ≤7.9% [n=29], Midrange 8.0-8.8% [n=34], High ≥8.9% [n=29]). There are 93 instead of 94 participants because there was limited long-term HbA1c data (5 years) available for one participant. This participant is included in analyses that do not depend on a value for mean HbA1c. Group comparison on demographic, diabetes and health variables are presented. The three mean HbA1c groups (Low, Midrange, High) did not differ by gender, IQ, education, age, age of onset of diabetes, duration of diabetes, anxiety, or depression (Table 5.2). Groups were compared on their mean performance for all cognitive tests. Results are provided in Table 5.3.

Table 5.2 *Comparison of Demographic Variables Between Mean HbA1c Groups*

Variable	Mean HbA1c Group			Significance
	Low HbA1c ≤7.9 % mean (SD)	Midrange HbA1c 8.0-8.8% mean(SD)	High HbA1c ≥8.9% mean(SD)	
	n=29	n=34	n=29	
Gender[a]	Female=13 Male=16	Female=19 Male=15	Female=17 Male=13	$\chi^2(2)=1.05$, $p=0.59$
Age[b]	57.57(7.7)	58.55(9.32)	59.79(9.45)	$F(2,90)=.462$, $p=0.63$
NART-IQ[b]	3.14 (1.2)T 115(6.6)UT	3.09 (.87)T 116(5.2)UT	3.61 (1.1)T 112(8.2)UT	$F(2,90)=2.31$, $p=0.11$ (T)
Education[c]	48.95	50.29	41.38	$H(2)=1.98$, $p=0.37$
Age of Onset[b]	26.11(9.96)	24.57(9.4)	29.63(13.8)	$F(2,90)=1.69$, $p=0.19$
Duration of Diagnosis[b]	31.46 (10.5)	33.98 (12.1)	30.15(12.9)	$F(2,90)=0.84$, $p=0.43$
HADS Anxiety[c]	47.45	44.93	48.92	$H(2)=.36$, $p=0.83$
HADS Depression[c]	39.29	48.22	53.07	$H(2)=4.02$, $p=0.13$

a.Chi Square analysis (χ^2): group numbers indicated for each HbA1c level.

b.ANOVA analysis(F): mean and standard deviation indicated for each HbA1c level.

c.Kruskal Wallis non-parametric analysis (H): mean rank indicated for each HbA1c level.

Note. Transformations were used for analysis of NART-IQ (Reverse & Square Root) and because of a non-normal distribution of this variable. For ease of understanding, the means displayed for both the untransformed variable (UT) and the transformed variable (T) with the associated F score.

Table 5.3 *ANOVA Results for Cognitive Tests by Mean HbA1c Group*

Cognitive Tests	Mean HbA1c Group: Low HbA1c ≤7.9% Mean (SD) n=29	Midrange HbA1c 8.0-8.8% Mean (SD) n=34	High HbA1c ≥8.9% Mean (SD) n=30 (n=29 TMT)	*F*	*p*
A-ELCC	.040 (.91)	.197 (.83)	-.267 (1.1)	1.98	.144
TMT AZ	.865 (.37) T	1.02 (.28) T	.98 (.34) T	1.90	.156
TMT BZ	.981 (.49) T	1.23 (.40) T	1.08 (.45) T	2.46	.091
SRI Z	.012 (.65)	.050 (.96)	-.008 (.68)	.045	.956
SRD Z	.145 (.68)	.021 (.88)	.030 (.13)	.251	.779
SDMT-W Z	-.433 (1.2)	-.175 (.97)	-.311 (.97)	.469	.627
SDMT-O Z	-.196 (1.24)	.076 (.944)	.123 (1.1)	.748	.476
Digit Span Z	1.38 (.35) T	1.49 (.36) T	1.35 (.38) T	1.48	.233

A-ELCC=Age-Adjusted Estimate of Lifetime Cognitive Change; TMT = Trail Making Test; SRI = Story Recall Immediate; SRD = Story Recall Delayed; SDMT-W/SDMT-O= Symbol Digit Modalities Test Written (W)/ Oral (O).

N.B. Transformations (indicated by T) were used for analysis of TMT A & B and Digit Span Z scores (Square Root) because of a non-normal distribution of these variables. For consistency and ease of comparison across tests the transformed TMT scores were reversed to be in line with the other cognitive test scores for which a lower score is related to poorer performance.

Results indicated no significant differences between groups based on the omnibus F test for any cognitive measure. Hypothesis testing was completed through planned comparisons and a trend was identified for age-adjusted lifetime cognitive change (A-ELCC). Planned comparisons revealed that the High mean HbA1c group showed a trend towards a lower A-ELCC score, than the Midrange mean HbA1c group, $t(90)=1.97$, $p=.052$, two-tailed, $d=.42$. The A-ELCC score for

the High mean HbA1c group was below 0, suggesting relative cognitive decline ($\bar{x}$= -.27, SE=.20). In comparison, the A-ELCC score for the Midrange HbA1c group was above 0, indicating cognitive stability or improvement ($\bar{x}$=.20, SE=.14). Although the score for the High mean HbA1c group was below 0, this score was within one standard deviation of the mean indicating overall performance was still within the average range of functioning.

Alternative Measures of HbA1c and Cognitive Function

Relationship with Mean HbA1c. Pearson correlation was used to examine the relationship between current HbA1c (value on test date) and recent HbA1c (frequency weighted mean most recent 5 years) and a frequency weighted standard deviation (HbA1c SD) between measures, with measures of diabetes health and with measures of cognitive function (Appendix O). The measures of HbA1c are highly interrelated. Mean HbA1c was correlated with current HbA1c (r=.580, p=.000), recent HbA1c (r=.826, p=.000), and HbA1c standard deviation (r=.492, p=.000) with the highest correlation value for the 5 year measure of HbA1c. This indicates limited differentiation between the long-term and recent mean values of HbA1c with more differentiation from the current value of HbA1c.

Relationship with Diabetes Complications. All HbA1c values have a relationship with measures of diabetes complications. Higher current HbA1c is related to higher retinopathy (r_s=.274, p =.004) and total microvascular disease (r=.202, p =.026) although not duration of

diagnosis (r=.003, p =.49) nor age of onset(r=-.002, p =.49). Higher recent HbA1c is related to higher retinopathy (r_s=.333, p=.001) and total microvascular disease (r=.350, p=.000) and not duration of diagnosis (r=-.020, p =.42) nor age of onset (r=.029, p =.39). In comparison, mean HbA1c has a slightly stronger relationship with both retinopathy (r_s=.365, p=.000) and total microvascular disease (r=.470, p=.000) and also does not have a significant relationship with duration of diagnosis (r=-.050, p =.32) nor age of onset (r=-.024, p =.41). HbA1c SD was not related to any of these diabetes health variables or measures of diabetes burden. HbA1c based on long-term period shows a relatively stronger relationship with diabetes complications suggesting it is, among the three measures, the best indicator of overall diabetes health.

Relationship with Cognitive Processes. Results of Pearson correlation indicated both current and recent HbA1c were correlated to scores on a test of immediate story recall, whereas mean HbA1c was not. Higher current HbA1c (r=.186, p=.02) and higher recent HbA1c (r=.172, p=.049) were both significantly related to higher scores on immediate story recall, with a slightly stronger correlation for current HbA1c. Mean HbA1c was not correlated with immediate story recall (r=.091, p=.19) and ANOVA results (Table 5.7) indicated no significant differences between Low, Midrange and High HbA1c groups. Episodic memory is an area that has not been highlighted in previous T1DM research.

HbA1c Group Comparison of Cognitive Processes. Both current HbA1c and recent HbA1c were split into the same three groups based on HbA1c value (Low=≤7.9%, Midrange = 8.0-8.8%, High≥8.9%). As a result, many participants changed groups (Table 5.4). For current HbA1c, 55 percent of participants stayed in the same group to which they were assigned based on mean HbA1c (51/93). Forty-five percent of participants (42/93) moved up or down one or two groups. For recent HbA1c, 63 percent of participants stayed in the same group to which they were assigned based on mean HbA1c (59/93). Thirty-seven percent of participants (34/93) moved up or down one or two groups. Although there is moderate correlation between alternative measures of HbA1c, changing the definition of HbA1c based on current or more recent values made a notable change of group assignment, affecting over one third of the group as originally defined by a 10-year frequency weighted HbA1c. The choice of how to measure HbA1c has not been of particular concern in previous T1DM research (i.e. choice of long-term or short-term value is not explained), but appears to affect potential group composition and therefore would likely lead to different results.

Table 5.4 *Number and Percentage of Participants With Change in Mean HbA1c Group Based on Alternative HbA1c Measurement*

HbA1c Measure	Same	Change 1 Group		Change 2 Groups	
		Up	Down	Up	Down
Current HbA1c	51	22	13	3	4
Percentage	54.8%	23.7%	14.0%	3.2%	4.3%
Recent HbA1c	59	18	12	2	2
Percentage	63.4%	19.4%	12.9%	2.2%	2.2%

Total n=93

ANOVA was used to examine the relationship between current and recent HbA1c group and demographic variables (Table 5.5 & Table 5.6). There was a significant difference between groups for NART IQ and years of education when using current HbA1c. These two variables were controlled in analyses using current HbA1c. There were no significant differences between groups on demographic variables using recent HbA1c; therefore no control variables were required.

Table 5.5 *Comparison of Demographic Variables Between Current HbA1c Groups*

Variable	Current HbA1c Group: Low HbA1c ≤7.9 %	Midrange HbA1c 8.0-8.8%	High HbA1c ≥8.9%	Significance
	n=32	n=37	n=25	
Gender[a]	Female=16 Male=16	Female=22 Male=15	Female=11 Male=14	$\chi^2(2)=1.52$, $p=.47$
Age[b]	58.84(8.8)	58.83(8.16)	58.18(9.94)	F (2,91) =.05, $p=.95$
NART-IQ[b]	3.02 (1.1)T 116(5.6)UT	3.09 (.996)T 115(4.9)UT	3.86 (.92)T 110 (7.3)UT	F (2,91) =5.94, $p=.004$ (T)**
Education[c]	52.48	51.82	34.72	$H(2)=7.59$, $p=.022$*
Age of Onset[b]	25.26(8.96)	29.23(12.9)	25.14(10.94)	$F(2,91) = 1.45$, $p=.24$
Duration of Diagnosis[b]	33.58 (11.20)	29.62 (12.05)	33.04(12.75)	$F(2,91) =1.11$, $p=.34$
HADS Anxiety[c]	48.13	48.85	44.70	$H(2)=.375$, $p=.83$
HADS Depression[c]	45.63	46.11	51.96	$H(2)=.933$, $p=.63$

a.Chi Square analysis (χ^2): group numbers indicated for each HbA1c level.
b.ANOVA analysis(F): mean and standard deviation indicated for each HbA1c level.
c.Kruskal Wallis non-parametric analysis (H): mean rank indicated for each HbA1c level. Note. Transformations were used for analysis of NART-IQ (Reverse & Square Root) because of a non-normal distribution of this variable. For ease of understanding the means displayed for both the untransformed variable (UT) and the transformed variable (T) with the associated F score. *$p<.05$, **$p<.01$

Table 5.6 *Comparison of Demographic Variables Between Recent HbA1c Groups*

Variable	Recent HbA1c Group			Significance
	Low HbA1c ≤7.9 %	Midrange HbA1c 8.0-8.8%	High HbA1c ≥8.9%	
	n=33	n=33	n=28	
Gender[a]	Female=17 Male=16	Female=15 Male=18	Female=17 Male=11	$\chi^2(2)=1.42$, $p=.49$
Age[b]	58.01(8.4)	59.29 (8.8)	58.69(9.4)	F (2,91) =.17, p=.84
NART-IQ[b]	3.07 (1.1)T 115(6.7)UT	3.15 (.96)T 115(5.9)UT	3.64 (.997)T 112(7.6)UT	F (2,91) =2,59, p=.08
Education[c]	51.30	52.12	37.57	$H(2)$=5.37, p=.068
Age of Onset[b]	25.66(9.29)	26.30(13.0)	28.69(11.27)	$F(2,91) = .596$, p=0.55
Duration of Diagnosis[b]	32.36 (11.61)	33.0 (12.58)	29.99(11.88)	$F(2,91) =.513$, p=0.60
HADS Anxiety[c]	48.36	45.83	48.45	$H(2)$=.192, p=.91
HADS Depression[c]	43.30	47.82	52.07	$H(2)$=1.60, p=.45

a.Chi Square analysis (χ^2): group numbers indicated for each HbA1c level. b.ANOVA analysis(F): mean and standard deviation indicated for each HbA1c level. c.Kruskal Wallis non-parametric analysis (H): mean rank indicated for each HbA1c level. Note. Transformations were used for analysis of NART-IQ (Reverse & Square Root) because of a non-normal distribution of this variable. For ease of understanding, the means displayed for both the untransformed variable (UT) and the transformed variable (T) with the associated F score.

ANOVA was used to investigate the relationship between HbA1c level and results on the different cognitive tasks. There were no differences between groups using either current or recent HbA1c on the age-adjusted estimate of lifetime cognitive change (A-ELCC), the oral version of Symbol Digit Modalities (SDMT-O), Story Recall-Delayed or the Trail Making Tests (TMT-A & B). Mean HbA1c will be used in multiple regression focused on these cognitive processes.

Results of the ANOVA and ANCOVA using Story Recall Immediate (SRI) and Delayed (SRD), including mean HbA1c, recent HbA1c and current HbA1c, are shown in Table 5.7. Overall ANCOVA results (controlling for education and NART IQ) are significant only for current HbA1c and SRI. There is a trend towards a significant difference between the current HbA1c groups on SRD. Planned comparisons revealed that the low current HbA1c group showed significantly lower scores on the SRI test ($\bar{x}$=-.26, SE=.13) than the high current HbA1c group ($\bar{x}$=.33, SE=.16), $t(89)$=-2.83, p=.006. As well, planned comparisons revealed that the low current HbA1c group showed significantly lower scores on the SRD test ($\bar{x}$=-.17, SE=.13) than the high current HbA1c group ($\bar{x}$=.32, SE=.15), $t(89)$=-2.40, p=.018. The score for the low current HbA1c group was below the mean (0) for both SRI and SRD, but within one standard deviation based on the normative sample, indicating average performance. When comparing across means, qualitatively, using mean HbA1c, the High group has the lowest SRI score, whereas for both the recent and current HbA1c groupings the low group has the lowest SRI score. Current

values of HbA1c were used in the multiple regression for this cognitive process.

Table 5.7 *ANOVA and ANCOVA Results for Story Recall Immediate (I) and Delayed (D) by HbA1c Group (Mean, Recent and Current)*

	HbA1c Group				
	Low HbA1c ≤7.9%	Midrange HbA1c 8.0-8.8%	High HbA1c ≥8.9%	*F*	*p*
Mean HbA1c Group Number	n=29	n=34	n=30		
Story Recall I Mean (SD)	.012 (.65)	.050 (.96)	-.008 (.68)	.045	.956
Story Recall D Mean (SD)	.145 (.68)	.021 (.88)	.030 (.69)	.251	.779
Recent HbA1c Group Number	n=33	n=33	n=28		
Story Recall I Mean (SD)	-.14 (.78)	.13 (.70)	.06 (.84)	1.03	.362
Story Recall D Mean (SD)	-.02 (.74)	.14 (.68)	.06 (.86)	.361	.698
Current HbA1c Group Number	n=32	n=37	n=25		
Story Recall I Mean (SE)	-.255 (.13)	.036 (.12)	.332 (.16)	4.08	.020*
Story Recall D Mean (SE)	-.170 (.13)	.081 (.12)	.317 (.15)	2.97	.057

* $p<.05$. Note. ANCOVA controlling years of education and NART IQ used in comparing current HbA1c groups.

The Digit Span Test ANOVA results (Table 5.8) indicate that there were differences between recent HbA1c groups, $F(2,91)=8.26$,

p=.001, d=.29. Planned comparisons indicate that the high recent HbA1c group showed lower mean Digit Span performance ($\bar{x}$=1.28, SD=.37) than the midrange recent HbA1c group ($\bar{x}$=1.60, SD=.35), t(91)=3.716, p=.000, two-tailed, d=.78. There were no overall differences on Digit Span when using current HbA1c, F(2,89)=1.68, p=.192 controlling for NART IQ and education. When mean HbA1c was used, there were also no differences between groups, F(2,90)=1.48, p=.23. All scores on the Digit Span task were greater than one standard deviation above the mean indicating better than average performance on this task in comparison to the normative sample. Recent HbA1c values will be used in the multiple regression analysis for this cognitive process.

ANOVA results indicated no difference between groups on the Symbol Digit Modalities Test-Written (SDMT-W) for either recent HbA1c groups, F(2,90)=1.72, p=.19, or the current HbA1c groups, F(2,89)=.77, p=.47 (Table 5.9). Planned comparisons did however reveal a trend towards lower scores for the low recent HbA1c group ($\bar{x}$ =-.513, SD=1.15) than the high recent HbA1c group ($\bar{x}$ =-.014, SD=1.16), t(90)=-1.65, p=.052, d=-.35, controlling for unequal variance (Levene Statistic=3.98, p<.05). These scores were within one standard deviation below the mean of the normative population indicating average performance.

Table 5.8 *ANOVA Results for Digit Span by HbA1c Group (Mean, Recent and Current)*

	HbA1c Group				
	Low HbA1c ≤7.9%	Midrange HbA1c 8.0-8.8%	High HbA1c ≥8.9%	*F*	*p*
Mean HbA1c Group Number	n=29	n=34	n=30		
Digit Span Mean (SD)	1.38 (.35)	1.49 (.36)	1.35 (.38)	1.48	.233
Recent HbA1c Group Number	n=33	n=33	n=28		
Digit Span Mean (SD)	1.33 (.29)	1.60 (.35)	1.28 (.37)	8.26	.001*
Current HbA1c Group Number	n=32	n=37	n=25		
Digit Span Mean (SE)	1.33 (.06)	1.46 (.05)	1.45 (.07)	1.68	.192

NB Digit span z scores were transformed (square root) for analysis.

Table 5.9 *ANOVA Results for Symbol Digit Modalities - Written by HbA1c Group (Mean, Recent and Current)*

	HbA1c Group				
	Low HbA1c ≤7.9%	Midrange HbA1c 8.0-8.8%	High HbA1c ≥8.9%	*F*	*p*
Mean HbA1c Group Number	n=29	n=34	n=30		
SDMT-Written Mean (SD)	-.433 (1.2)	-.17(.97)	-.311 (.97)	.469	.627
Recent HbA1c Group Number	n=33	n=33	n=27		
SDMT-Written Mean (SD)	-.513 (1.15)	-.319 (.759)	-.014 (1.17)	1.722	.185
Current HbA1c Group Number	n=32	n=37	n=24		
SDMT-Written Mean (SE)	-.439 (.18)	-.314 (.16)	-.089 (.21)	.768	.467

5.6.2. Measures of Diabetes Health

The influence of measures of diabetes health (i.e. retinopathy, microvascular disease, insulin resistance, severity of hypoglycaemia) and measures of disease burden (duration of diagnosis, age of onset) has been investigated for their relationship with cognitive deficit in previous T1DM studies (Brands et al., 2005). In this study, results of Spearman's rho correlation indicate that higher severity of retinopathy is related to lower scores on the age-adjusted estimate of lifetime cognitive change (A-ELCC), r_s=-.188, p=.04, a test of perceptual speed,

Trail Making Test-A (TMT-A), *r*=-.227, *p* =.014 and a test of executive function, Trail Making Test-B (TMT-B), *r*=-.187, p =.04). Results of this study showed that higher severity on a measure of total microvascular disease was also related to lower scores on age-adjusted estimate of lifetime cognitive change (A-ELCC), *r*=-.209, *p*=.02, TMT-A (*r*=-.258, *p*=.006), TMT-B (*r*=-.264, *p*=.005), Symbol Digit Modalities – Written (SDMT-W), *r*=-.307, *p*=.001, and Symbol Digit Modalities-Oral, *r*=-.275, *p*=.004. An estimate of insulin resistance (eGDR) and self-rating of average number of hypoglycaemic events per year which required assistance did not show significant correlation with any cognitive task. Having diabetes for a longer duration was related to lower scores on the TMT-A (*r*=-.205, *p*=.02), the TMT-B (*r*=-.238, *p*=.01) and SDMT-O (*r*=-.172, *p*=.049). Although earlier age of onset is correlated with longer duration of diagnosis (*r*=-.715, *p*=.000) in this study, age of onset was not correlated with any of the cognitive tests. The diabetes health variables with significant correlations to cognitive tests are explored further.

Retinopathy and Microvascular Disease

Higher severity of retinopathy and a higher combined rating of microvascular disease are correlated with lower scores in some cognitive domains including perceptual speed, executive function and estimated lifetime cognitive change, as indicated above. ANOVA was used to compare groups varying on severity of retinopathy (Mild/Observable; Referable; Proliferative) on the cognitive tests.

ANOVA was used to compare retinopathy groups on demographic variables (Table 5.10).

Table 5.10 *Comparison of Demographic Variables Between Retinopathy Severity Groups*

Variable	Retinopathy Group			Significance
	Mild/ Observable	Referable	Proliferative	
	n=40	n=21	n=33	
Gender[a]	Female=20 Male=20	Female=12 Male=9	Female=17 Male=16	$\chi^2(2)=.289$, $p=.86$
Age[b]	55.85(8.4)	60.80 (7.66)	60.72 (9.21)	F (2,91) =3.78, $p=.026$*
NART-IQ[b]	3.21 (1.0)T 115(5.7)UT	3.23 (1.04)T 115(7.9)UT	3.37 (1.16)T 113 (7.5)UT	F (2,91) =.24, $p=.79$ (T)
Education[c]	52.33	47.38	41.73	$H(2)=2.77$, $p=.25$
Age of Onset[b]	26.43(11.47)	33.48(11.32)	22.96(9.07)	F(2,91) = 6.28, p=.003**
Duration of Diagnosis[b]	33.58 (11.20)	29.62 (12.05)	33.04(12.75)	F(2,91) =1.11, $p=.34$
HADS A[c]	55.08	49.31	37.17	$H(2)=8.03$, $p=.018$*
HADS Depression[c]	51.29	52.93	39.45	$H(2)=4.56$, $p=.102$

a.Chi Square analysis (χ^2): group numbers indicated for each HbA1c level.

b.ANOVA analysis(F): mean and standard deviation indicated for each HbA1c level.

c.Kruskal Wallis non-parametric analysis (H): mean rank indicated for each HbA1c level.

Note. Transformations were used for analysis of NART-IQ (Reverse & Square Root) because of a non-normal distribution of this variable. For ease of understanding, the means displayed for both the untransformed variable (UT) and the transformed variable (T) with the associated F score. *$p<.05$, **$p<.01$

Results indicated that there were differences between retinopathy groups in age, F(2,91)=3.78, p=.026, with the mild/observable retinopathy group younger ($\bar{x}$=55.85, SD=8.4) than the proliferative retinopathy group ($\bar{x}$=60.71, SD=9.2, p<.05), based on Tukey HSD post hoc test. There was also a difference between retinopathy groups in age of onset, F(2,91)=6.28, p=.003, with the referable retinopathy group showing later age of onset (mean = 33.48, SD=11.3) than the mild/observable group ($\bar{x}$ = 26.43, SD=11.5, p=.042) and the proliferative group ($\bar{x}$= 22.96, SD=9.1, p=.002), based on Tukey HSD post hoc test. Finally there was a difference between retinopathy groups based on anxiety level, H(2)=8.00, p=.018. Post-hoc testing using Mann-Whitney U indicated that the proliferative retinopathy group (Mean Rank =29.09) showed significantly lower anxiety ratings than the mild/observable retinopathy group (Mean Rank=43.53), U=399, p=*.004*, r=-0.34. Lower anxiety may lead to an advantage for the proliferative retinopathy groups on cognitive tasks, as such it is not a factor that would lower cognitive scores in this group. The relationship between and anxiety, diabetes health variables and cognitive test results will be further explored in the chapter on psychological variables (Chapter 7). As well, all cognitive scores have already been adjusted for age. Only age of onset will be used as a covariate in ANCOVA.

Results of the ANOVA for cognitive function, controlling for age of onset are displayed in Table 5.11.

Table 5.11 *Results Of ANOVA Comparison Of Cognitive Tests By Retinopathy Level Controlling for Age of Onset*

Cognitive Tests	Retinopathy Level			*F*	*p*
	Mild/ Observable Mean (SE)	Referable Mean (SE)	Proliferative Mean (SE)		
	n=40	n=21	n=33 (n=32 TMT)		
A-ELCC	.304 (.15)	-.252 (.21)	-.174 (.17)	3.42	.037*
TMT AZ	1.03 (.05) T	.942 (.07) T	.878 (.06) T	2.07	.132
TMT BZ	1.21 (.07) T	1.07 (.10) T	.991 (.08) T	2.21	.115
SRI Z	-.014 (.12)	.055 (.18)	.026 (.14)	.058	.944
SRD Z	.059 (.12)	.148 (.17)	.001 (.13)	.213	.809
SDMT-W Z	-.186 (.17)	-.211 (.239)	-.498 (.19)	.834	.438
SDMT-O Z	.156 (.17)	.199 (.24)	-.309 (.19)	2.00	.141
Digit Span Z	1.42 (.06)T	1.30 (.08) T	1.47 (.06) T	1.28	.282

A-ELCC=Age-Adjusted Estimate of Lifetime Cognitive Change; TMT = Trail Making Test; SRI = Story Recall Immediate; SRD = Story Recall Delayed; SDMT-W/SDMT-O= Symbol Digit Modalities Test Written (W)/ Oral (O)

N.B. Transformations (indicated by T) were used for analysis of TMT A & B and Digit Span Z scores (Square Root) because of a non-normal distribution of these variables. For consistency and ease of comparison across tests the transformed TMT scores were reversed to be in line with the other cognitive test scores for which a lower score is related to poorer performance.

It was expected that those with highest severity retinopathy would show the poorest cognitive performance compared to those with lower severity of retinopathy. Both the Referable and Proliferative Retinopathy groups showed an age-adjusted estimate of lifetime cognitive change (A-ELCC) score below 0, indicating a decline in cognitive function from estimated premorbid IQ. In contrast the

Mild/Observable Retinopathy group showed a mean A-ELCC score above 0 indicating stability or improvement from an estimate of premorbid IQ. There was a significant difference between groups that varied on retinopathy severity for the mean A-ELCC, $F(2,88)=4.438$, $p=.015$, shown in Figure 5.1, when controlling for age, age of onset of diabetes and anxiety rating.

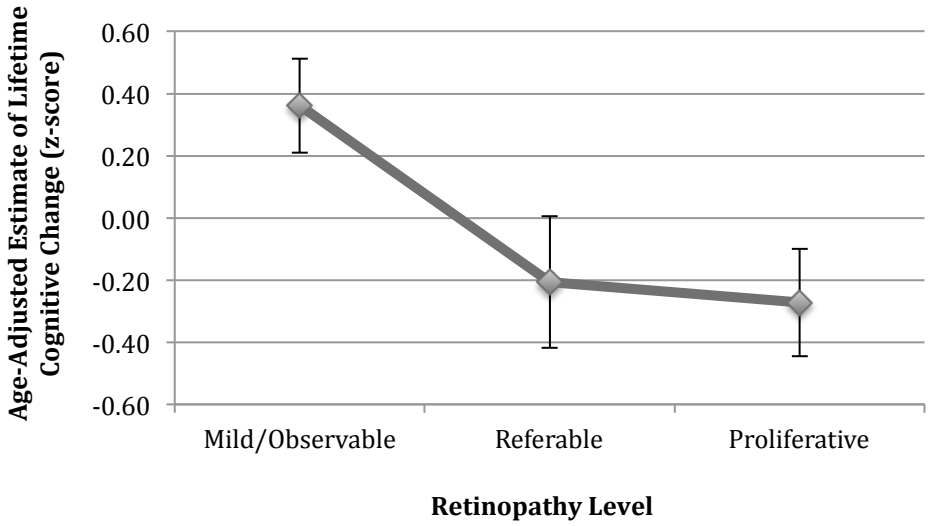

Figure 5.1. Mean age-adjusted estimate of lifetime cognitive (A-ELCC) change z score by retinopathy group controlling for age, age of onset, and anxiety.

Planned comparison indicated that the Proliferative retinopathy group showed lower mean A-ELCC score ($\bar{x}$=-0.27, SE=.17), than the mild/observable retinopathy group ($\bar{x}$=0.36, SD=.15), $t(88)=2.66$, $p=.009$). The score for the referable retinopathy group ($\bar{x}$=-0.21, SD=.21) was not different from that of the proliferative retinopathy group.

Results of omnibus F test indicated no significant difference between retinopathy groups on a test of perceptual speed, TMT A, $F(2,89)=2.07$, $p=.13$, however planned comparisons indicated a significant difference between the proliferative retinopathy group ($\bar{x}$ =.878, SE=.06) and the mild/observable retinopathy group, ($\bar{x}$=-1.03, SE=.05), $t(89)=2.01$, $p=.048$. Similarly, there was no overall significant difference between groups on a test of executive function, TMT-B, F(2,89)=2.22, $p=.115$, however planned comparisons indicated that the proliferative retinopathy group showed weaker performance ($\bar{x}$ =.991, SE=.08), than the mild/observable retinopathy group, ($\bar{x}$=1.21, SE=.07), $t(89)=-2.06$, $p=.043$.

No significant differences were found between groups on mean scores for a test of perceptual speed (SDMT-O & W) or on the tests of verbal episodic memory, Story Recall Immediate or Delayed or short-term/working memory (Digit Span).

Retinopathy and mean HbA1c

Higher mean HbA1c is correlated with higher retinopathy (r_s=.365, p =.000), and greater overall microvascular disease (r_s =.470, p =.000). Could it be that HbA1c is related to cognitive deficits through its relationship with these complications? Factorial ANOVA was used to look the possible interaction between severity of retinopathy and level of mean HbA1c. Because of low group numbers, the retinopathy group was split into two – those with no/mild/observable retinopathy (Lowest Retinopathy; n=39) and those with referable/proliferative retinopathy (Highest Retinopathy; n=54). The HbA1c groups remained

the same (Low, n=29; Midrange n=34; High, n=30). The total number is 93 instead of 94 because there was no mean HbA1c data for 1 participant. Group size was uneven with a significant discrepancy confirmed by chi square analysis, $\chi^2(2)=6.20$, p=.045, two-tailed, in frequency of group membership, likely reflecting the discrepancy between the size of the Lowest and Highest retinopathy groups with High HbA1c (Table 5.12).

Table 5.12 *Group Size for Factorial ANOVA Mean HbA1c (3) and Retinopathy Severity (2)*

	Mean HbA1c Group			
Retinopathy	Low	Midrange	High	Total
Severity	≤7.9%	8-8.8%	≥8.9%	
Lowest	17	14	8	39
Highest	12	20	22	54
Total	29	34	30	93

When considering the age-adjusted estimate of lifetime cognitive change (A-ELCC), there was a significant main effect based on retinopathy group, $F(1,87)=5.661$, $p=.020$ with the highest retinopathy group showing a lower A-ELCC score ($\bar{x}$=-.195, SD=.13) than the lowest retinopathy group ($\bar{x}$=.287, SD=.16). The mean A-ELCC score for the highest retinopathy group was below 0, indicating decline from estimated premorbid IQ, whereas the score for the lowest retinopathy group was above 0 indicating overall stability or improvement from estimated premorbid IQ levels. There was a no significant effect of

HbA1c group on mean A-ELCC score, $F(2,87)=.786$, $p=.46$. Although, there was no significant interaction between severity of retinopathy and mean HbA1c, $F(2,87)=.734$, $p=.48$, planned comparisons revealed that those within the highest retinopathy group who also had high mean HbA1c showed a lower mean A-ELCC score ($\bar{x}=-.482$, SD=1.12) than those in the lowest retinopathy group who also had high mean HbA1c ($\bar{x}=.323$, SD=.672), $F(1,89)=7.21$, $p=.009$. Results are displayed in Figure 5.2. These groups are much different in size, with only 8 in the lowest retinopathy/high HbA1c group compared to 22 in the highest retinopathy/high HbaA1c group. However, the estimates for mean A-ELCC score for the lowest retinopathy group are nearly identical across all mean HbA1c groups despite the larger size of the midrange mean HbA1c group (n=14) and the low mean HbA1c group (n=17), suggesting that more participants would not necessarily have significantly influenced the level of mean performance for this particular group. Furthermore, there is a numerically smaller variance in scores for the lowest retinopathy group with high mean HbA1c (SD=.67) than for those in the highest retinopathy group with high mean HbA1c (1.12) indicating greater consistency between scores in the former group. This also suggests a higher group number would not necessarily influence the outcome for this group on this variable. Post Hoc Tukey tests indicated no other significant differences between mean A-ELCC scores. In the Highest retinopathy group, those with Midrange HbA1c achieved a mean above 0, indicating stability or improvement from an estimate of premorbid IQ. Those groups with low

and high mean HbA1c groups achieved means below 0 indicating decline from an estimate of premorbid IQ suggesting that when high levels of retinopathy are present both extremes of blood glucose may increase risk of cognitive decline.

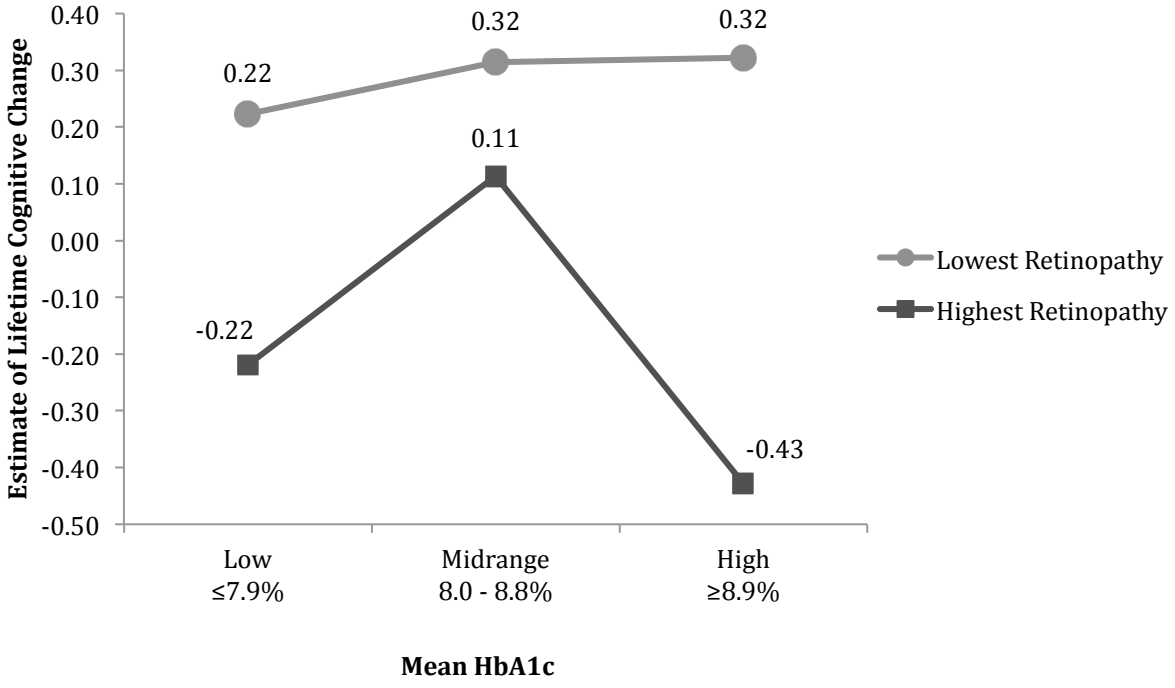

Figure 5.2. Mean age-adjusted estimate of lifetime cognitive change by mean HbA1c group and retinopathy severity.

On a test of processing speed, Trail Making Test-A (TMT-A), factorial ANOVA indicated a main effect of mean HbA1c, $F(2,86)=3.16$, $p=.047$. Planned comparisons indicate that the low mean HbA1c group shows lower mean score on TMT-A ($\bar{x}=.84$, SE=.060) than the high mean HbA1c group ($\bar{x}=1.03$, SE=.056), $p<.05$. There was also a significant effect of retinopathy level, $F(1,86)=6.17$, $p=.015$, with those in the highest retinopathy group showing a lower mean score on TMT-A ($\bar{x}=.877$, SE=.045) than those in the lowest

retinopathy group ($\bar{x}$=1.05, SE=.054). There was no significant interaction between mean HbA1c group and retinopathy level, $F(2,86)=1.13$, $p=.327$. However, there was a trend towards a difference between TMT-A scores for those in the Low HbA1c group depending on the retinopathy group, $F(1,88)=3.84$, $p=.053$, with those in the highest retinopathy group ($\bar{x}$=.701, SD=.318) showing a lower mean TMT A score than those in the lowest retinopathy group ($\bar{x}$=.982, SD=.362). Possibly highlighting a degree of vulnerability for those with low mean HbA1c as well. These scores are above the mean and well within the average range.

On a test of executive function, the Trail Making Test B (TMT-B), factorial ANOVA indicated a main effect of mean HbA1c, $F(2,86)=3.32$, $p=.041$. However, planned comparisons indicate no significant differences between the High mean HbA1c group and the Low or midrange mean HbA1c groups. There was a non-significant interaction between mean HbA1c group and retinopathy level, $F(2,86)=.084$, $p=.92$. There were no differences in mean HbA1c scores based on level of retinopathy or vice versa.

5.6.3. General Health Variables and Cognitive Function

Question 2: Is cognitive function related to general health variables and health promoting habits?

People with diabetes are also at increased risk general health variables (i.e. hypertension, high cholesterol, high BMI). Could it be that people with relatively weaker cognitive function have greater general health variables or differ in health promoting habits (i.e.

exercise, cognitive activity)? To investigate this possibility, non-parametric correlation Spearman's rho was used to determine if there were any significant relationships between cognitive function and these health factors outlined in Table 5.13. Significant correlations are highlighted below. One-tailed correlation significance was used. The complete correlation table is provided in Appendix O.

Table 5.13 *General Health Variables for Analysis of Cognitive Impairment*

Cardiovascular	**Cholesterol**	**Obesity**	**Health Habits**
Systolic BP	Total Cholesterol	BMI	Exercise (Less/Same/More)
Diastolic BP	HDL Cholesterol	Waist/Hip Ratio	Rate of Perceived Exertion (Low to moderate / Strong)
	Triglycerides		Cognitive Activity (Less/Same/More)

Results of Spearman's rho correlation indicate that higher self-rating on a perceived exertion scale, when participants rated how much they typically exert themselves in physical activity on a scale of 1 to 10, correlated with a better age-adjusted estimate of lifetime cognitive change score (A-ELCC), r_s =.237, p =.02. Results of partial correlation indicate that this relationship was maintained when controlling for participant education, pr_s =.247, p=.012, NART-IQ, pr_s =.236, p=.015, or age, pr_s =.234, p=.015.

Greater self-reported daily cognitive activity in comparison to age peers was related to higher scores on Digit Span, a task of short-

term/working memory, r_s =222, p =.02 and higher IQ scores, r_s =.182, p =.04. The relationship between the task of short-term/working memory and the self-rating of cognitive activity becomes a non-significant trend when controlling for NART-IQ, pr_s =.165, p=.057.

Higher HDL (good) cholesterol levels were related to lower scores on the Digit Span test, r_s =-.175, p =.046, however this became a non-significant trend when controlling for participant age, pr_s=-.168, p=.054. Story Recall Delayed (SRD) had a negative relationship with waist-hip ratio, r_s=-.177, p=.046, however this relationship became non-significant when controlling for participant age, pr_s =-.138, p=.097 and NART-IQ, pr_s=-.102, p=.17. Given that many of these correlations values that became non-significant when considering other factors, these general health variables and health promoting habits were not included as predictors in further analysis.

5.6.4. Question 3

Which diabetes health variables have the strongest predictive value on cognitive function?

Finally, measures of diabetes health and diabetes burden found significant in the preceding analyses or influential in previous studies were entered into a multiple regression analysis to determine which factors were best at predicting cognitive function (i.e., A-ELCC, TMT-A & B, SDMT-O &W, SRI, SRD and Digit Span). Using backward stepwise entry with an exclusion criteria of p<.055, age, female gender, NART-IQ, retinopathy/micovascular disease,

mean/recent/current HbA1c, severe hypoglycaemia, and duration of diagnosis were entered into the multiple regression analysis. Predictors were limited due to the number of subjects and issues of multicollinearity between predictors (e.g. duration of diagnosis and age of onset; retinopathy and microvascular disease; education and IQ; mean/recent/current HbA1c). In this case, one predictor was chosen if it had the highest correlation with cognitive function. Based on the finding of significant correlation (Appendix O), the dichotomous variable retinopathy was used as the predictor in the analysis of age-adjusted estimate of lifetime cognitive change. For all other cognitive tests, microvascular disease had the strongest correlation with these tests and was therefore used in these regression analyses instead of retinopathy. Age of diagnosis was left out of the final analysis given its high correlation with duration of diagnosis and the fact it loaded on the same dimension when it was included in the model, causing a problem of multicollinearity. Age of diagnosis was not correlated with any of the cognitive domains tested (Appendix O). Duration of diagnosis is included in the regression as it is correlated with scores on the Trail Making Test – A (r=-.205, p <.05), Trail Making Test-B (r=-.238, p <.05) and Symbol Digit Modalities (r=-.172, p <.05). Although severe hypoglycaemia was not found to be a significant predictor of cognitive deficit it was included due to the relationship between lower mean HbA1c levels and an increased risk of hypoglycaemia (Cryer, 2010).

The results of the final 2 steps of this analysis for each cognitive test are presented in Table 5.14. The best predictors of the age-adjusted estimate of lifetime cognitive change (A-ELCC) were retinopathy, severe hypoglycaemic events and female gender, explaining 17% of the variability in the A-ELCC score (r^2=.174). These variables were retained as significant predictors in the final step of the model and is a significant predictor of cognitive change (A-ELCC), F(1,91)=6.017, *p*=.001, with a combination of higher retinopathy (*ß*=-.259, *t*(89)=-2.671, *p*=.009), female gender (*ß*=-.290, *t*(89)=-2.962, *p*=.004), and higher frequency of hypoglycaemic events (*ß*=-.201, *t*(89)=-2.049, *p*=.043) predictive of a lower A-ELCC z score.

Total microvascular disease burden was found to be the sole predictor on processing speed tasks. Microvascular disease was retained as a significant predictor in the final step of the model and is a significant predictor of the TMT-A score, F(1,90)=8.53, *p*=.004, with a higher level of microvascular disease related to lower TMT-A score (*ß*=-.294, *t*(90)=-2.92, *p*=.004). However, this factor on its own explains a small percentage (8.7%) of the TMT-A score (r^2=.087).

The best predictor on another test of perceptual speed, Symbol Digit Modalities – Oral (SDMT-O) is a combined score for microvascular disease. Microvascular disease was retained as a significant predictor in the final step of the model and is a significant predictor of the SDMT-O score, F(1,90)=8.02, *p*=.006) with higher microvascular disease score related to lower SDMT-O score (*ß*=-.286,

t(90)=-2.833, *p*=.006). However, this factor on its own explains a small percentage (8.2%) of the SDMT-O score (r^2=.082).

The best predictor on a written version of Symbol Digit Modalities – Written (SDMT-W) is a combined score for microvascular disease. Microvascular disease was retained as a significant predictor in the final step of the model and is a significant predictor of the SDMT-W score, F(1,90)=10.26, *p*=.002, with higher microvascular disease score related to lower SDMT-W score (*ß*=-.320, *t*(90)=-3.202, *p*=.002). However, this factor on its own explains a small percentage (10.2%) of the SDMT-W score (r^2=.102).Total microvascular disease has a slightly stronger relationship to the written version of the SDMT which required a paper and pencil response in the form of writing the numbers corresponding with the symbols, than the oral version of the SDMT, which only required saying the numbers corresponding with the symbols. The best predictors of the episodic memory scores were current HbA1c and NART-IQ. Together, these variables accounted for 13.5% of the variance in SRI scores, F(1,90)=7.10, *p*=.001, r^2=.135, and 13.1% of the variance in SRD scores, F(1,90)=6.87, *p*=.002, r^2=.131.

Table 5.14 *Predictors of Scores on Tests of Cognitive Processing*

Cognitive Test	Predictors	*B*	S.E.	Beta	*F*	*p*	R^2
A-ELCC[a]	(Constant)	-.264	.642			.682	
Step 4	Age	.009	.011	.080		.434	
	Female Gender	-.558	.186	-.295		.004	
	Retinopathy	-.538	.194	-.281		.007	
	Hypo 2	-.371	.188	-.195	4.648	.052	.174
A-ELCC	(Constant)	.744	.200			.000	
Step 5	Female Gender	- .549	.185	-.290		.004	
	Retinopathy	-.496	.186	-.259		.009	
	Hypo 2	-.383	.187	-.201	6.017	.043	.169
TMT-A[b]	(Constant)	1.173	.074			.000	
Step 6	Female Gender	-.095	.066	-.161		.154	
	Micro Total	-.231	.076	-.307	5.348	.003	.107
TMT-A	(Constant)	1.116	.063			.000	
Step 7	Micro Total	-.221	.076	-.294	8.526	.004	.087
TMT-B[b]	(Constant)	-1.591	.910			.084	
Step 3	Age	-.009	.005	-.178		.096	
	Female	-.163	.087	-.181		.063	
	NART-IQ	.022	.007	.338		.001	
	Micro Total	-.252	.116	-.245		.033	
	Mean HbA1c	.115	.055	.218	5.201	.042	.232
TMT-B	(Constant)	-1.615	.919			.083	
Step 4	Female	-.184	.087	-.204		.037	
	NART-IQ	.019	.006	.283		.005	
	Micro Tot	-.320	.110	-.311		.005	
	Mean HbA1c	.109	.056	.207	5.675	.054	.207

Table 5.14 (cont.)

Cognitive Test	Predictors	*B*	S.E.	Beta	*F*	*p*	R^2
SDMT[b]	(Constant)	-3.048	1.814		.	096	
Step 6	NART-IQ	.028	.015	.184		.072	
	Micro Tot	-.667	.242	-.279	6.923	.007	.135
SDMT	(Constant)	.242	.199			.227	
Step 7	Micro Tot	-.765	.239	-.320	10.255	.002	.102
Digit Span[c]	(Constant)	-1.233	.566		.	.032	
Step 5	Female	-.079	.067	-.110		.241	
	NART-IQ	.024	.005	.444	12.056	.000	.209
Digit Span	(Constant)	-1.276	.566			.027	
Step 6	NART-IQ	.024	.005	.444	22.622	.000	.197
SRI[d]	(Constant)	-6.224	1.638			.000	
Step 5	NART-IQ	.038	.012	.334		.002	
	Current HbA1c	.206	.073	.288		.006	
	Duration	.006	.006	.093	5.034	.341	.144
SRI	(Constant)	-6.005	1.621			.000	
Step 6	NART- IQ	.038	.012	.332		.002	
	Current HbA1c	.205	.073	.288	7.100	.006	.135
SRD[d]	(Constant)	-5.591	1.580			.001	
Step 5	Age	-.010	.009	-.117	.	.248	
	NART-IQ	.041	.012	.375		.001	
	Current HbA1c	.183	.071	.264	5.046	.012	.144
SRD	(Constant)	-5.766	1.576			.000	
Step 6	NART-IQ	.038	.011	.346		.001	
	Current HbA1c	.177	.071	.255	6.868	.015	.131

a. age, female, NART-IQ, retinopathy (low/high), mean HbA1c, duration, severe hypo (low/high)
b. age, female, NART-IQ, microvascular total, mean HbA1c, duration, severe hypo (low/high)
c. age, female, NART-IQ, microvascular total, recent HbA1c, duration, severe hypo (low/high)
d. age, female, NART-IQ, microvascular total, current HbA1c, duration, severe hypo (low/high)

On the test of cognitive flexibility (TMT-B) demographic variables (female gender & NART-IQ) emerged as the significant predictors along with total microvascular disease. Mean HbA1c was retained in the final model, but was just below the threshold for significance. These factors explain 20.9% of the variance in TMT-B score (r^2=.209). Microvascular disease was retained as a significant predictor in the final step of the model and is a significant predictor of the TMT-B score, F(1,90)=5.68, *p*=.000, with a higher level of microvascular disease related to lower TMT-B score (*ß*=-.311, *t*(87)=-2.907, *p*=.005) along with NART-IQ (*ß*=.283, *t*(87)=-2.869, *p*=.005) predictive of higher TMT-B score and female gender (*ß*=-.204, *t*(87)=-2.116, *p*=.037), predictive of lower TMT-B score. This task also has a perceptual speed component, joining alternating numbers and letters as quickly as possible with a pencil line. The only significant predictor remaining for the working memory task, Digit Span, was NART-IQ, explaining 19.7% of the variance in this score, F(1,90)=22.62, *p*=.000.

5.7. Discussion

5.7.1. Question 1

Do individuals who differ on glycaemic control and other diabetes health variables show significantly different scores on measures of cognitive processes?

Results showed that severity of microvascular disease, specifically retinopathy, was the diabetes health variable that most consistently differentiated group scores on the cognitive processing measures. Those with proliferative retinopathy showed lower scores than those with low levels of retinopathy on an estimate of lifetime cognitive change, processing speed, and executive function (set-shifting). These areas are typically found to differentiate the T1DM group from control groups (Brands et al., 2005). This is consistent with findings that retinopathy was identified as one of the key predictors of cognitive change in a large longitudinal study (Jacobson et al., 2011). When retinopathy was evaluated together with glycaemic control, it was noted that severity of retinopathy also led to greater vulnerability to the extremes of glycaemic control. Those with proliferative retinopathy and the highest level of mean HbA1c showed the greatest decline on the estimate of lifetime cognitive change. There was a trend for those with proliferative retinopathy and the lowest level of mean HbA1c on processing speed.

Dividing the group based mean HbA1c on its own did not indicate differences on cognitive processing scores. The is in line with results of other cross-sectional studies (Brismar et al., 2007; Zihl et

al., 2010). Using alternative measures (recent and current) highlighted the importance of the particular measurement of HbA1c on the results. Those with low current HbA1c showed lowest scores on the measures of episodic memory. Those with high recent HbA1c showed lowest scores on short term/working memory. Those with low recent HbA1c showed a trend towards the lowest scores on a measure of processing speed. This suggests that there may be disadvantages at both extremes of HbA1c for this older group that has not been highlighted in studies of younger adult groups (Jacobson et al., 2007, 2011).

Results also highlight the potential that differences in motor speed rather than cognitive processing may have influenced some of the findings from studies in groups with T1DM. Based on previous studies, it was expected that a differentiation in performance based on mean HbA1c would especially be apparent on tasks of processing speed (Brands et al., 2006; Jacobson et al., 2007 & 2011;). However, the tasks used in this study did not have as strong a motor component as ones used in some previous studies that required a more complex fine motor control, specifically fitting a small key in a hole in Grooved Pegboard (Lafayette Instrument Co., 2002). Fine motor speed may be especially important to take into consideration with older adults groups who would have greater incidence of peripheral nerve damage. In fact, neuropathy and measures of nerve conduction have been highlighted as predictors of cognitive function in previous studies (Ryan, 2005; Brismar et al. 2007). It may be that the difference between those with T1DM and controls in the DCCT/EDIC study (Jacobson et al., 2007 &

2011) is based more on a difference in physical motor speed rather than cognitive processing speed.

It is important to note that cognitive results emphasized that all relative deficits in cognitive processing scores were within the average range based on age within the study group. This indicated that differences highlighted between groups were mild. Differences in cognitive measure and differences how HbA1c is measured may explain differences in results of cognitive studies in this group. More emphasis will need to be placed on differentiating these factors in future studies to gain a clear picture of the impact of HbA1c on cognitive processes.

5.7.2. Question 2

Is cognitive function related to indicators of general health variables and health promoting habits?

Results of this study indicate that greater perceived exertion in exercise was correlated to higher scores on the estimate of lifetime cognitive change even when considering IQ, education and age. Cognitive research studying the T1DM group has not yet included potential cognitive protective factors. There is some evidence that exercise has a positive influence on cognitive function. Cotman & Berchtold (2002) suggest that exercise has molecular and cellular effects that influence brain plasticity, especially in ageing. In a review of the available literature, Kramer, Bherer, Colcombe, Dong, & Greenough (2004), conclude that the results are mixed as to the effects of factors such as fitness on preserving cognitive function into old age. Although, protective factors have not been studied in T1DM studies of

cognition, these factors have been investigated in some studies of T2DM and cognition with some initial support. Bruce and colleagues (2008), in a prospective study of cognitive change after 7 years, found that engaging in any amount of exercise in the past two weeks was a protective factor against cognitive decline in an older T2DM group. The identification of the relationship between higher perceived exertion and a higher estimate of cognitive change (less decline) in the study group suggests that exercise may be a potential modifiable factor that can be advised in the treatment of adults with T1DM.

There were no markers of general health related to cognitive processes when taking into consideration other factors like premorbid IQ. Although some previous studies have identified general health variables as predictors of cognitive function in such as BMI and hypertension (Brismar et al., 2007; Brands et al., 2006) as well as cardiovascular events in longitudinal analysis of older samples (Van Duinkerken, 2011), other studies have not found strong evidence for measures of macrovascular health implicated in cognitive change over the long-term (Jacobson et al., 2011). It may be that because the study group is middle aged and older, the presence of pre-cursors of cardiovascular disease are common across the whole group and some of these health factors are controlled by medication (e.g. blood pressure and cholesterol), reducing the importance of these variables in differentiating cognitive performance between groups.

5.7.3. Question 3

Which diabetes health variables have the strongest predictive value on cognitive function?

When diabetes health variables and demographic characteristics were combined in analysis, retinopathy or microvascular disease were found to be the strongest predictors in many cognitive processing areas including the estimate of lifetime cognitive change, all measures of processing speed and executive function. This finding is in line with previous studies. Retinopathy and renal disease were identified as independent predictors of cognitive change scores over time in a large longitudinal study (Jacobson et al., 2011), however mean HbA1c was also identified as being and independent predictor of cognitive function, unlike results of this study. Other microvascular diseases including neuropathy have also been identified as a significant predictor of cognitive scores (Brismar et al., 2007).

Results indicated that mean HbA1c was not an independent predictor of cognitive differences in a group of middle-aged to older adults with T1DM. This is in line with results of the cognitive study by Brismar and colleagues (2007) and the conclusion of a study of adults over age 50 (Brands et al., 2006) indicating that chronic exposure to hyperglycaemia was not sufficient to have considerable structural impact on the brain. Although mean HbA1c is not an independent predictor of cognitive function, current HbA1c and NART-IQ were the best predictors of episodic memory scores. This aspect of memory has not been highlighted in other T1DM research, however this may be a

cognitive process more important in ageing populations and appears to be related to the particular measure of HbA1c chosen (i.e. current value).

Results showed that a higher frequency of self-reported severe hypoglycaemic events was identified as a significant predictor of estimated lifetime cognitive change (A-ELCC). Previous findings that recurrent hypoglycaemia relayed no long-term risk in cognitive functioning is based on a large prospective study of relatively younger adults (Jacobson et al., 2007 & 2011). However, this was consistent with recent findings from a prospective study that older adults with frequent severe hypoglycaemic events were more likely to show cognitive decline (Van Duinkerken et al., 2011) and the suggestion that older adults may be more vulnerable to this factor. There may be risks for older adults with T1DM in cognitive functioning at both extremes of glycaemic control that are not apparent at younger ages. Maintaining glycaemic control near normal, with the trade-off of more frequent hypoglycaemic events may have some negative cognitive outcomes for this group.

5.7.4. Conclusions

What do the results tell us about cognitive ageing in T1DM and its relationship with theories of healthy cognitive ageing?

Study results indicate that middle aged and older individuals with T1DM perform at a level that is within the average in relation to the information on the normative population for these tests. Overall, their performance does not distinguish them as deficient as a group in

comparison to their age peers. Although differences were identified in cognitive processing for groups with greater severity of microvascular disease, measures of current and recent HbA1c, and recurrent hypoglycaemia, relative deficits were within the average range. This indicates that there are not evident signs of early cognitive ageing based on results of cognitive testing within the group as a whole. This is in line with the finding that only moderate cognitive deficits were identified between older groups with T1DM and controls (Van Duinkerken, 2011; Brands et al., 2006). Although the group did not show significant deficits overall, further examination of the participants in the cognitive study who did show cognitive processes significantly below the mean will be investigated to determine whether there may be a higher incidence of mild cognitive impairment (MCI) in the sample compared to the general population and the diabetes health variables that are predictive of MCI in Chapter 6. Increased incidence of MCI especially in the middle-aged adults with T1DM would provide evidence of early cognitive ageing in this group.

The maintenance of cognitive performance is present despite evidence from structural brain imaging of adolescents with T1DM that deficits in gray and white matter are identified even from a young age (Perantie et al., 2007). The cognitive reserve theory indicates that maintenance of cognitive function despite brain insults is accomplished through strong neural networks and neural compensation, or use of alternative brain networks when the ones typically used begin to fail (Stern, 2009). Similarly, STAC theory posits that the brain uses

scaffolding to compensate for structural brain changes in an effort to maintain cognitive function (Park & Reuter-Lorenz, 2009). According to these theories, cognitive performance may be maintained through functional brain changes that could be detected using functional MRI (fMRI). This means that it is possible early or accelerated brain ageing may be occurring even when cognitive function is maintained. Accelerated cognitive ageing has been dismissed as a possibility in groups with T1DM (Ryan, 2005); however, this conclusion is based only on cognitive testing. Research on cognitive ageing provides evidence that maintenance of cognitive function can occur even though there are signs of brain ageing (Reuter-Lorenz & Park, 2010). Identification of predictors of cognitive function provides targets for group comparison in fMRI that are most likely to show functional brain changes. Severity of microvascular disease, retinopathy in particular, was the most common predictor of differences across cognitive processing tasks. Groups were constructed based on high and low severity of retinopathy for comparison in the fMRI study presented in Chapter 8.

Chapter 6
Mild Cognitive Impairment

6.1. Introduction

The presence of mild cognitive impairment (MCI) has been identified as a factor that increases a person's risk for developing dementia later in life (Petersen, 2011). It signifies a marked deviation from the course of the normal cognitive ageing process. In a recent review, Petersen (2011) reports that for groups over 65, the prevalence rate for MCI is between 10 to 20%. Other researchers have reported an incidence rate from 3 to 19% (Gauthier et al., 2006). Meta-analysis of prospective population studies of people with diabetes have indicated a 1.5 to 2 times higher risk of Alzheimer's disease and a 2 to 2.5 times higher risk of vascular dementia, however the proportion of people with T1DM in these studies is not specified and will primarily be a T2DM population due to the higher incidence of this disease in the diabetes population (Biessels et al., 2006). Given the higher risk of MCI in prospective population studies of diabetes and the association with factors common in T1DM such as insulin use, long duration, early onset and complications, it was hypothesized that those with T1DM may also show an increased incidence of MCI. If greater MCI is present in this primarily middle-aged study sample, this would provide evidence of early cognitive ageing in this group.

6.2. Study Aims

This investigation explored the evidence for MCI within the total

cognitive study sample (n=94) based on presence of objective cognitive impairment greater than 1.5 SD below the mean for age. Although having a diagnosis of MCI was an exclusion criteria in the study sample, there were still individuals who displayed deficits in areas of cognitive function that would meet the objective criteria for MCI. The study set out to explore whether the group who could be identified with MCI was different from those who show lower levels of cognitive impairment or no cognitive impairment in systematic ways that would explain the differences (i.e. older age, lower education, lower IQ) and whether this group would show indications of diabetes health variables (i.e. more microvascular complications, chronic hyperglycaemia, recurrent hypoglycaemic events, greater insulin resistance) or greater disease burden (i.e. longer duration, earlier onset) as in previous studies of MCI in primarily T2DM populations.

6.3. Study Questions

1. *What is the incidence and nature of MCI in the study sample? How does this compare to the incidence of MCI in the general population?*
2. *Are there differences in the age, education or general intelligence of the participants in the study sample who show MCI in comparison to those who show lower levels of cognitive impairment?*

3. *Are there differences in general health variables and health habits in those who show MCI in comparison to those who show lower levels of cognitive impairment?*
4. *Are there differences in diabetes health variables for those with MCI and in comparison to those who show lower levels of cognitive impairment? What are the strongest predictors of MCI?*

6.4. Methods

6.4.1. Identification of MCI

Petersen (2004) distinguishes between MCI with memory deficits, a-MCI, amnestic type with memory only (single domain) or with other cognitive deficits (multiple domain), and those with a cognitive impairment in a cognitive area other than memory na-MCI or non-amnestic in a single domain or multiple domains. Petersen (2004) indicates that these different variations of MCI have different levels of risk for advancing to Alzheimer's or other types of dementia, with the presence of amnestic types of MCI increasing risk of Alzheimer's and vascular dementia and the non-amnestic types of MCI more commonly a precursor of other types of dementia (e.g. fronto-temporal dementia and dementia with lewy bodies) although other researchers have found that these distinctions in type of MCI do not predict types of dementia accurately (Fischer et al., 2007). Petersen (2004) proposes several criteria to define amnestic type MCI :

- Memory complaint usually corroborated by an informant
- Objective memory impairment for age

- Essentially preserved general cognitive function
- Largely intact functional activities
- Not demented

(Petersen, 2004,p.189)

Petersen (2004) suggests that a cutoff to determine an objective cognitive impairment compared to age in previous studies has been greater than 1.5 SD below the mean for age, however he cautions that this is to be used in conjunction with the other criteria. Other research groups have operationalized this objective impairment to greater than 1.0 SD below the mean (Ganguli, Dodge, Shen, & DeKosky, 2004). Petersen (2004) also describes non-amnestic MCI, which includes objective cognitive impairment in any other cognitive domainThe criteria for MCI include five components. Some of the evidence for meeting these criteria is primarily subjective or self-rated and other evidence is primarily objective or age norm-referenced. Table 6.1 provides the MCI criteria adapted from Peterson (2004). In this table, the MCI criteria are divided into type (subjective or objective) and operationalized by providing the evidence necessary to meet each criterion. Subjective cognitive complaints were not assessed as explained below.

Table 6.1 *Operationalized Criteria for Mild Cognitive Impairment*

Criteria for MCI	
Subjective	Objective (Norm-Referenced)
1. **Person complains of memory and/or other cognitive difficulties** (cognitive complaints are noted be the person themselves and may or may not be noticed by others)	1. **Presence of an objective cognitive impairment**. (memory or other cognitive function in at least one area greater than 1.5 SD below mean for age)
2. **Intact functional activities** (person reports that they can perform general activities of daily living independently or dependence is solely due to physical disability)	2. **Preserved general cognitive function** (evidence of average to above average IQ for age - rule out that the reason for impairment is below average cognitive function)
	3. **No Dementia** (rule out those who meet norm-referenced criteria for dementia)

*based on amnestic MCI criteria, Petersen (2011; 2004)

Objective Cognitive Impairment. Results of the cognitive study provided detailed information about the presence of objective cognitive impairment in the study sample, the key inclusionary objective criteria

for MCI. The percentage of participants who meet this criteria, could be verified by examining participants' cognitive function level in relation to age across various domains including memory, processing speed, executive function, and an estimate of cognitive change. In the literature, evidence of objective cognitive impairment has been defined in research by using an inclusion value starting at greater than 1 SD below the mean (Ganguli et al., 2004), however it is more common to use a strict inclusion value of greater than 1.5 SD below the mean (Petersen, 2011) to diagnose MCI.

Preserved General Cognitive Function. In the present study, all participants have preserved general cognitive function. Specifically, all participants had average to above average general intelligence (i.e. NART IQ within 1 SD of the mean or > 1SD above the mean).

Intact Functional Activities. Information on functional activities was not specifically collected; however, all participants lived independently (i.e. in their own home) and maintained primary responsibility for their own diabetes care (i.e. insulin injections, blood glucose monitoring).

No Dementia. A diagnosis of dementia was an exclusion criteria for the study, and as such no participant in the study was diagnosed with dementia. A diagnosis of MCI was also an exclusion criteria, however, some participants showed cognitive impairment in cognitive testing.

Subjective Cognitive Complaints. There was evidence that components of the subjective MCI criteria were met, but this was not confirmed. In particular, information on subjective cognitive complaints were not systematically collected and only provided in anecdotes by some participants. Some researchers do not believe this is an essential component of the diagnosis of MCI and rather view this factor as an indicator of higher risk for progression of MCI to dementia (Mitchell, 2008a; Mitchell, 2008b).

6.4.2. Statistical Analysis

To answer these questions, age norm-referenced z scores for each participant in the total study sample (n=94) were counted as meeting the minimal objective criteria for cognitive impairment (CI) if the z score was greater than 1SD below the mean in any cognitive domain. The nature of the cognitive impairments was defined for this group by counting the number of participants who showed specific impairments in memory, processing speed, executive function or an estimate of cognitive change. A separate count was taken of participants who met the more strict criteria for objective cognitive impairment (CI), which is >1.5 SD below the mean for age (MCI). The characteristics of the MCI group were further explored and compared to the groups with Low CI (>1to 1.5SD below the mean) or no CI (within 1SD of the mean or above). Groups were compared on age, education, IQ, various diabetes health variables, and disease burden using group frequency measures (observation, and chi square). Spearman's Rho and Pearson correlation

were also used to examine the relationships between CI group, demographic, diabetes, and health variables. Groups representing the three levels of cognitive function (defined in Table 6.2) are compared using the general linear model (GLM) including correlation, ANOVA, and ANCOVA. Multiple regression is used to determine the best predictors of high cognitive impairment.

Table 6.2 *Groups for GLM Statistical Analysis*

Level of Cognitive Impairment Group Name and Group Size	Group Inclusion Criteria
MCI n=25	One or more cognitive domains > 1.5 SD below the mean for age
Low CI n=18	One or more cognitive domains > 1SD to 1.5 SD below the mean for age
No CI n=51	All cognitive domains within 1 SD or >1SD above the mean for age

Planned comparisons were completed irrespective of the significance of the *F*-test given that these comparisons are hypothesis driven based on the results of previous research and the number of planned comparisons (2) is one less than the number of groups (Karpinski, 2011).

6.5. Results

6.5.1. Question 1

What is the incidence and nature of MCI in the study sample?

Using the least strict criteria for cognitive impairment, a majority of participants of the total study sample (43 out of 94) showed at least one cognitive domain that was greater than 1 SD below the mean (46%). Of this group (n=43), 12 (28%) showed a memory impairment (story recall and/or digit span), 29 (67%) showed an impairment in processing speed (Trail Making Test A and/or Symbol Digit Modalities Test), 17 (40%) showed an impairment in executive function (Trail Making Test B) and 12 (28%) showed significant cognitive decline for age (A-ELCC). The percentage within each cognitive domain >1SD below the mean is displayed in Figure 6.1. The total percentage is greater than 100% of the group because 18 participants have impairment in two or more cognitive domains and were counted in each domain.

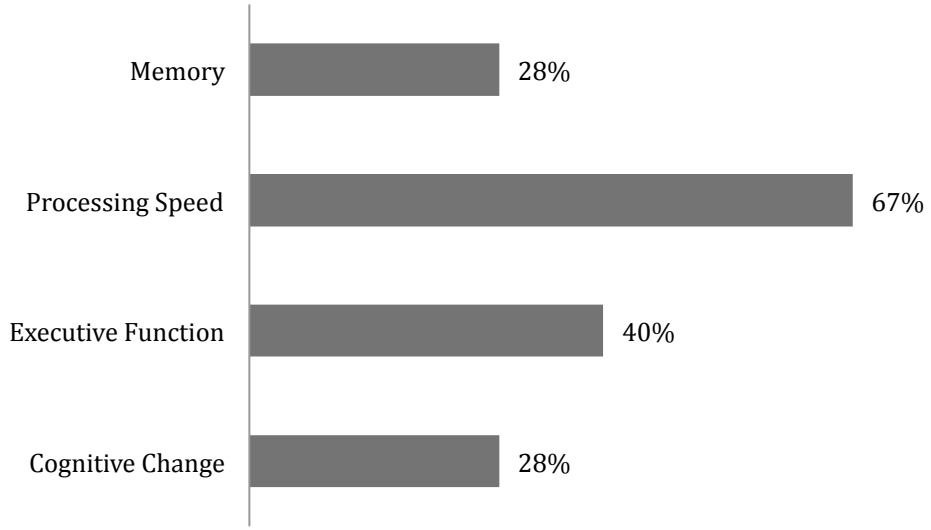

Figure 6.1. Percentage of participants with cognitive impairment (CI) greater than 1SD below mean (n=43) by cognitive domain.

Using the criteria for MCI recommended by Petersen (2011), objective cognitive impairment greater than 1.5 SD below the mean, 25 out of the total study sample of 94 (27%) met the criteria for an objective cognitive impairment. Of this subgroup 5 (20%) show impairment in the memory domain, 11 (44%) show impairment in processing speed, 14 (56%) in executive function, and 7 (28%) show evidence of cognitive decline. The percentage within each cognitive domain >1.5 SD below the mean is displayed in Figure 6.2. The total percentage is greater than 100% of the group (n=25) because 11 participants (44%) showed more than one area of objective cognitive impairment.

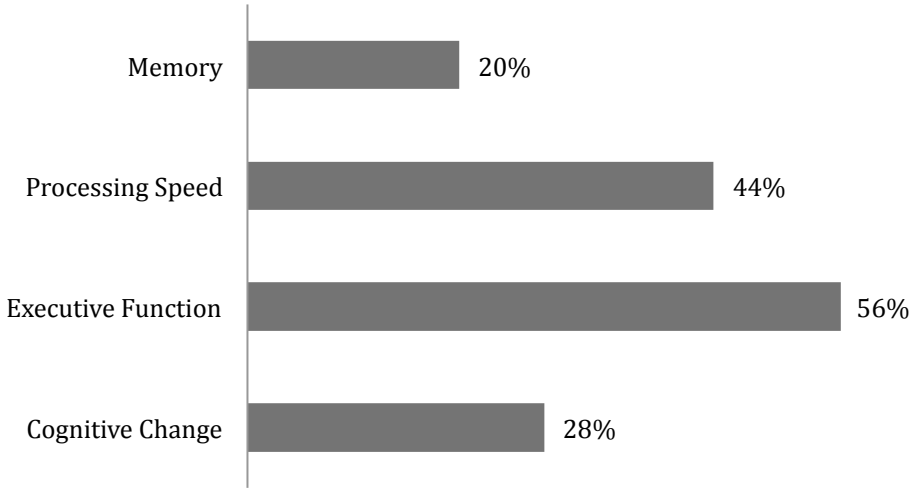

Figure 6.2. Percentage of participants with cognitive impairment (CI) greater than 1.5 SD below mean (n=25) by cognitive domain.

How does the incidence of MCI in the study sample compare to the incidence of MCI in the general population?

Twenty-seven percent of the sample met the objective criteria for cognitive impairment for the identification of MCI established by Petersen (2004). The total cognitive study sample ranges in age from 45 to just over 80, however the majority (81%) of this sample are under the age of 65 with a mean age of 58.7 years. MCI incidence is generally determined for those over 65 with an upper estimate of the incidence in the general population of 20% (Petersen, 2004). It is presumed there would be a lower incidence for middle-aged adults. In a normal distribution, under 7% of the population would have cognitive function >1.5 SD below the mean, indicating that this T1DM study population shows greater incidence of MCI than expected in the

general population. As well, the incidence of MCI (27%), for participants is slightly higher than the upper incidence of MCI reported in previous population research. These numbers may not be comparable as MCI was not confirmed in this study sample through direct confirmation of other diagnostic criteria, however, these participants would likely meet the full criteria for MCI as this relatively young group does meet the other objective criteria for MCI (i.e., no dementia and preserved general cognitive function) and meets subjective criteria for MCI (i.e. preserved daily functioning). The high rate of MCI in this primarily middle-aged sample suggests the possibility that there is a higher incidence of MCI generally in the T1DM population.

6.5.2. Question 2

Are there differences in age, education or general intelligence of the participants in the study sample who show MCI in comparison to those who show lower levels of cognitive impairment?

Could the group of participants who meet criteria for MCI show these impairments because they are older or have less years of education or lower intelligence than other participants?

Age

Eighty-four percent (21/25) of the group with objective cognitive impairment >1.5 SD below the mean (MCI, n=25), were under the age of 65. This was not different than the age distribution in the total study sample (n=94) with 81% under the age of 65. In addition, only 2 of the participants with multiple domains of high objective cognitive impairment in the sample (n=11) are over the age of 65 also suggesting

that advanced age is not the primary reason this group showed higher cognitive impairment.

The total study sample (n=94) was split into three groups that varied on incidence of objective cognitive impairment (No CI, Low CI and MCI) as indicated in Table 6.2. Correlation using Spearman's rho indicated that there is no relationship between age and CI group (r_s = .079, p =.46, two-tailed). ANOVA was also used to compare three groups on mean age. Results of this ANOVA are displayed in Table 6.3. The three groups do not differ in mean age, $F(2,91)=.20$, $p=.817$.

Table 6.3 *ANOVA Comparison of Mean Age and General Intelligence Between Cognitive Impairment Groups*

Demographic Factors	No CI Mean (SD) n=51	Low CI Mean (SD) n=18	MCI Mean (SD) n=25	*F*	*p*
Age	58.17 (9.2)	58.83 (8.1)	59.54 (8.7)	.203	.817
General Intelligence	2.95 (.80) T 117 (4.7) UT	3.56 (1.32) T 112 (7.8) UT	3.72 (1.1) T 111 (7.9) UT	5.91	.004*

*p<.01

N.B. General Intelligence variable was reversed and square root used to normalize the distribution for ANOVA. Transformed (T) means and standard deviations as well as untransformed (UT) means are used in the table to express data, along with the F score and significance relating to the transformation.

To determine whether the type of cognitive impairment (i.e., memory, executive function, processing speed or cognitive decline) in the MCI group was differentially distributed across participant age groups in the

whole study sample (n=94), the number of participants who could be classified under each domain was grouped into three age categories, under 55, 55 to 65 and over 65.

Table 6.4 provides information on a count of the number showing impairments in each cognitive area and the percentage of the total study sample (n=94) within each age group. Participants with multiple cognitive impairments were counted in more than one group.

Table 6.4 *Percentage of Participant Age Groups with Cognitive Processes Greater than 1.5SD Below The Mean*

Age Group n=total in whole group (94)	Memory n=5		Processing Speed n=11		Executive Function n=14		Age-Adjusted Cognitive Change n=7		Multiple Domains n=11	
	n	% of age group	n	% of age group	n	% of age group	n	% of age group	n	% of age group
Under 55 n= 37	2	5%	5	14%	6	16%	2	5%	5	14%
55-65 n=39	2	5%	4	10%	6	15%	4	10%	4	10%
Over 65 n=18	1	6%	2	11%	2	11%	1	6%	2	11%

There is a similar incidence of objective memory impairments across the age groups. Participants under age 55 showed a 3-4% higher incidence of impairment in processing speed than older participants. Participants under age 65 showed a 4-5% higher incidence of impairment in executive function than participants over age 65. The incidence of estimated cognitive decline was highest in the 55 to 65 year old age group. Those with multiple domains of cognitive impairment were found across all age groups, with a slightly higher (3-4%) incidence in the under 55 age group. Overall, participants showed the highest incidence of objective cognitive impairment in the areas of executive function and processing speed.

Education and Intelligence

Could the group with MCI have lower education or lower intelligence? The sample was divided into three groups that varied on incidence of objective cognitive impairment (No CI, Low CI, and MCI) as indicated in Table 6.2. Spearman's rho correlation was used to determine whether there was a relationship between education or general intelligence and CI. Groups were also compared on these variables using the Kruskal-Wallis Test (education) and ANOVA (general intelligence) to determine whether there were differences in general intelligence (IQ) between groups.

Regarding education, results show that the cognitive impairment groups did not differ in this factor. Spearman's rho correlation indicated that there was no significant relationship between years of education and CI group (r_s= -.162, p =.120, two-tailed). The result of the

Kruskal-Wallis non-parametric test is displayed in Table 6.5 for education, as this variable is not normally distributed. The three groups do not differ in years of education, $H(2)=2.67$, $p=.262$.

Regarding general intelligence, results show that the cognitive impairment groups did differ in this aspect. Spearman's rho correlation indicated that there is a significant relationship with general intelligence and CI group (r_s = -.374, p =.000, two-tailed). Results of the ANOVA are displayed in Table 6.3 for general intelligence. This analysis confirmed CI groups do differ on general intelligence, F(2,91)=5.91, p=.004. Post Hoc Tukey HSD comparison indicated that the MCI group had significantly lower mean IQ ($\bar{x}$ =111) than the No CI group ($\bar{x}$ =117), p=.001. Although lower, the mean IQ level in the MCI group is at the upper end of the average range, and does not suggest that there is a general intellectual deficit in this group.

Table 6.5 *Kruskal-Wallis Non-Parametric Comparison of Mean Rank of Education Between Cognitive Impairment Groups*

Demographic Factors	No CI Mean Rank (Mdn/SD)	Low CI Mean Rank (Mdn/SD)	MCI Mean Rank (Mdn/SD)	*H*	(*p*)
	n=51	n=18	n=25		
Education	50.95 (15.0/3.1)	47.94 (13.5 /4.2)	40.14 (12.0 /3.9)	2.67	.262

Note. In reporting Kruskal-Wallis the mean ranks used in the analysis along with the simple mean scores and standard deviations for comparison.

6.5.3. Question 3

Are there differences in general health variables and health habits in those who show high levels of objective cognitive impairment in comparison to those who show lower levels of objective cognitive impairment?

People with diabetes are also at increased risk for general health problems (i.e. cardiovascular disease, hypertension, high cholesterol). Could it be that people with MCI have poorer general health or differ health habits? To investigate this possibility, non-parametric correlation Spearman's rho was used to determine if there were any significant relationships between assignment to the cognitive impairment groups and obesity, cholesterol, or cardiovascular health indicators. Results of Spearman's rho correlation indicate no relationship between CI level and these general health variables shown in Table 6.6.

Table 6.6 *Spearman's Rho Correlation and Significance of Relationships Between General Health Variables and CI Group*

Variable	WHR	Systolic BP	Diastolic BP	High BP	BMI	Total Chol.	HDL Chol
CI Group	-.065 (.537)	.171 (.100)	-.006 (.958)	.097 (.353)	.018 (.860)	.058 (.576)	.043 (.678)

N.B. two-tailed significance values reported; CI Group = Cognitive Impairment Group; WHR = Waist Hip Ratio; Chol=Cholesterol; BMI=Body Mass Index

Results of T-Tests indicate that level of cognitive impairment (No CI vs MCI) was not related to measures of cardiovascular health, cholesterol levels shown in Table 6.7.

Table 6.7 *T-Test Comparison of Health Variables Between CI Groups*

Health Variables	No CI $\bar{x}$ *(SD)*	MCI $\bar{x}$ *(SD)*	*t (74)*	Sig. (*p*, 2-tailed)	Effect Size (*r)*
	n=51	n=25	§*df*=73		
	§n=50	§n=24	†*df*=72		
BMI[b]	1.43 (0.06)	1.43 (0.07)	-.175	.862	.020
Untransformed	26.90 (3.43)	27.23(4.84)			
Systolic BP	134.6 (15.71)	139.1 (13.17)	-1.22	.226	.14
Diastolic BP	72.86 (10.96)	72.96 (13.10)	-.034	.973	.004
Total Cholesterol[c]	2.10 (.18)	2.14 (.22)	-.862	.392	.10
Untransformed	4.46 (.77)	4.65 (.95)			
HDL Cholesterol	1.69	1.81	-1.05	.296	.12

Note: Transformations were used to normalize distribution for parametric testing: a. minimized one outlier to mean + 3SD; b. log transformation, c.square root transformation; Untransformed means and standard deviations were reported for Total Cholesterol and BMI for communicating in terms of a more easily understood metric.

Regarding health habits, higher cognitive impairment was related to lower cognitive activity (r_s =-.278, p=.007, two-tailed). This correlation remained when controlling for participant age, IQ and education through partial correlation, pr_s =-.248, p=.018, two-tailed. There was no significant relationship between greater self-reported exercise involvement to be related to lower levels of cognitive impairment, r_s =-.144, p =.12, two-tailed.

6.5.4. Question 4

Are there differences in diabetes health variables for those with MCI in comparison to those who show lower levels of cognitive impairment?

Could the group of participants with MCI show poorer diabetes health (i.e. more microvascular complications, higher mean HbA1c, more severe hypoglycaemic events, greater insulin resistance) or greater disease burden (i.e. longer duration, earlier onset)? This is expected based on the results of research in T2DM and MCI (Roberts et al., 2008) and consistent with the findings of the cognitive study. To answer this question, the sample was divided into three groups that varied on incidence of objective cognitive impairment (No CI, Low CI, and MCI) as indicated in Table 6.2. Spearman's rho correlation was used initially to determine any relationships between these variables and CI group. The results of this analysis are provided in Table 6.8.

Table 6.8 *Spearman's Rho Correlation and Significance of Relationships Between Diabetes Health Variables and CI Group*

Variable	Micro Total	Mean HbA1c	Hypos/ Year	Insulin Resist	Duration	Onset
CI Group	.372 (.000)**	.130 (.213)	.194 (.061)	-.061 (.561)	.210 (.042)*	-.162 (.120)

*=p<.05, (2-tailed), **=p<.01 (2-tailed)

N.B. CI Group = Cognitive Impairment Group; Micro Total = Combination score of retinopathy, neuropathy and nephropathy; Hypos/Year = Dichotomous variable of Low and High average number of severe hypoglycaemic events per year; Insulin Resist = Insulin Resistance based on estimated glucose disposal rate (eGDR).

The three cognitive impairment (CI) groups (No CI, Low CI and MCI) were also compared using ANOVA on diabetes health variables (i.e., microvascular disease, mean HbA1c, and insulin resistance) and indicators of disease burden (i.e., duration of diabetes and age of

onset). ANCOVA was used to control for variables that might influence significant relationships. Linear regression was used for the comparison of the categorical variable hypoglycaemic events with assistance per year. Microvascular disease, duration and age of onset were identified as factors related to MCI in previous research (Roberts et al., 2008). Hypoglycaemic events and insulin resistance were included as they are included as variables in this cognitive study. The results of the omnibus ANOVA tests are presented in Table 6.9. Results for each diabetes variable are discussed in turn.

Table 6.9 *ANOVA Comparison of Demographic and Diabetes Factors for Cognitive Impairment Groups*

Diabetes Factors	No CI Mean (SD)	Low CI Mean (SD)	MCI Mean (SD)	*F*	*p*
	n=51	n=18	n=25		
Microvascular Disease	.71 (.25) T	.84 (.33) T	.94 (.28) T	6.23	.003*
Mean HbA1c	8.3 (.77)	8.4 (.94)	8.7 (.96)	1.54	.220
Severe Hypo Events	.37 (.49)	.33 (.49)	.64 (.49)	3.01	.054
Insulin Resistance	.77 (.13) T	.72 (.12) T	.76 (.16) T	.946	.392
Duration of Diagnosis	30.21(11.77)	29.35(9.63)	37.1(11.98)	3.45	.036*
Age of Onset	27.8 (11.0)	29.5 (11.7)	22.4 (10.4)	2.77	.07

*$p<.05$ **$p<.01$;

Note. The variable "Microvascular Disease" transformed using square root used to normalize the distribution for ANOVA. The variable "Insulin Resistance used a Log 10 transformation. Transformed (T) means and standard are used in the table to express data, along with the F score and significance relating to the transformation. Severe Hypo Events is a dichotomous variable.

Microvascular Disease

A higher severity of microvascular disease has been related to the incidence of MCI in the T2DM population (Roberts et al., 2008). Results of the current study indicate a significant relationship between measures of microvascular disease and CI group. Higher cognitive impairment levels are related to higher severity of retinopathy (r_s = .224, p=.030, two-tailed) and a higher combined microvascular disease rating (r_s = .372, p=.000, two-tailed). The MCI group was compared to the No CI group on level of the microvascular disease retinopathy (none/mild, observable, referable, proliferative). The same divisions of retinopathy (Table 4.6) used in the cognitive study.

Figure 6.3 shows a comparison of the percentage of participants from the MCI (n=25) and No CI (n=51) groups categorized within each retinopathy severity level. A greater proportion of participants had proliferative retinopathy (highest severity) in the MCI group (56%) compared to the No CI group (24%). Results of chi square statistic indicated that there is a significant association between the level of cognitive impairment and level of retinopathy, $\chi^2(2)=8.22$, p=.016. This seems to represent the fact that there is a lower than expected frequency of participants in the No CI group with proliferative retinopathy and a greater than expected frequency of participants in the MCI group with proliferative retinopathy. The rates of mild/observable retinopathy were comparable in the two groups. A greater proportion of participants in the No CI group (29%) showed referable retinopathy (2^{nd} highest severity category) in comparison to the MCI group (12%).

There was a slightly higher than expected frequency of participants from the No CI group with referable retinopathy and a slightly lower than expected frequency of participants from the MCI group with referable retinopathy. There seemed to be a trade-off between the two highest severity categories of retinopathy (referable and proliferative), the MCI group with more participants in the highest of the two categories (proliferative) and the No CI group with more participants in the less severe of the two categories (referable).

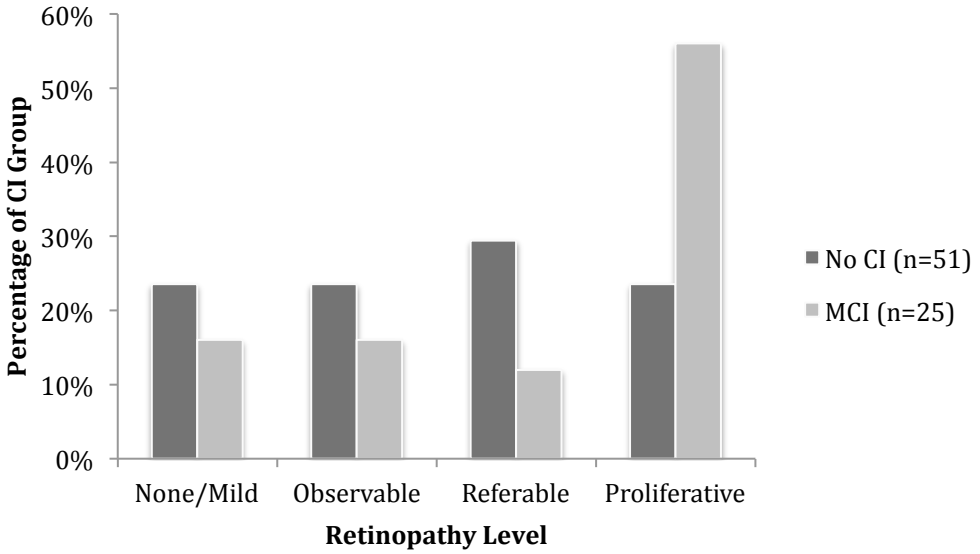

Figure 6.3. Percentage of participants at each retinopathy level in the MCI vs NO CI groups.

Results of ANOVA indicate a significant difference between groups with varying levels of cognitive impairment for total microvascular disease (combination of retinopathy, neuropathy and nephropathy), $F(2,91) = 6.23$, $p=.003$, with a medium effect size,

d=0.37. Planned comparison, assuming unequal variance, indicate that the MCI group showed a higher level of microvascular disease than the No CI group, $t(91)= -3.424$, $p=.001$, two-tailed, $d=0.76$ shown in Figure 6.4. The MCI group showed more severe levels microvascular disease than those participants with no cognitive impairment. There was a significant linear trend for microvascular disease severity across levels of cognitive impairment $F(1,91)=11.73$, $p<.01$.

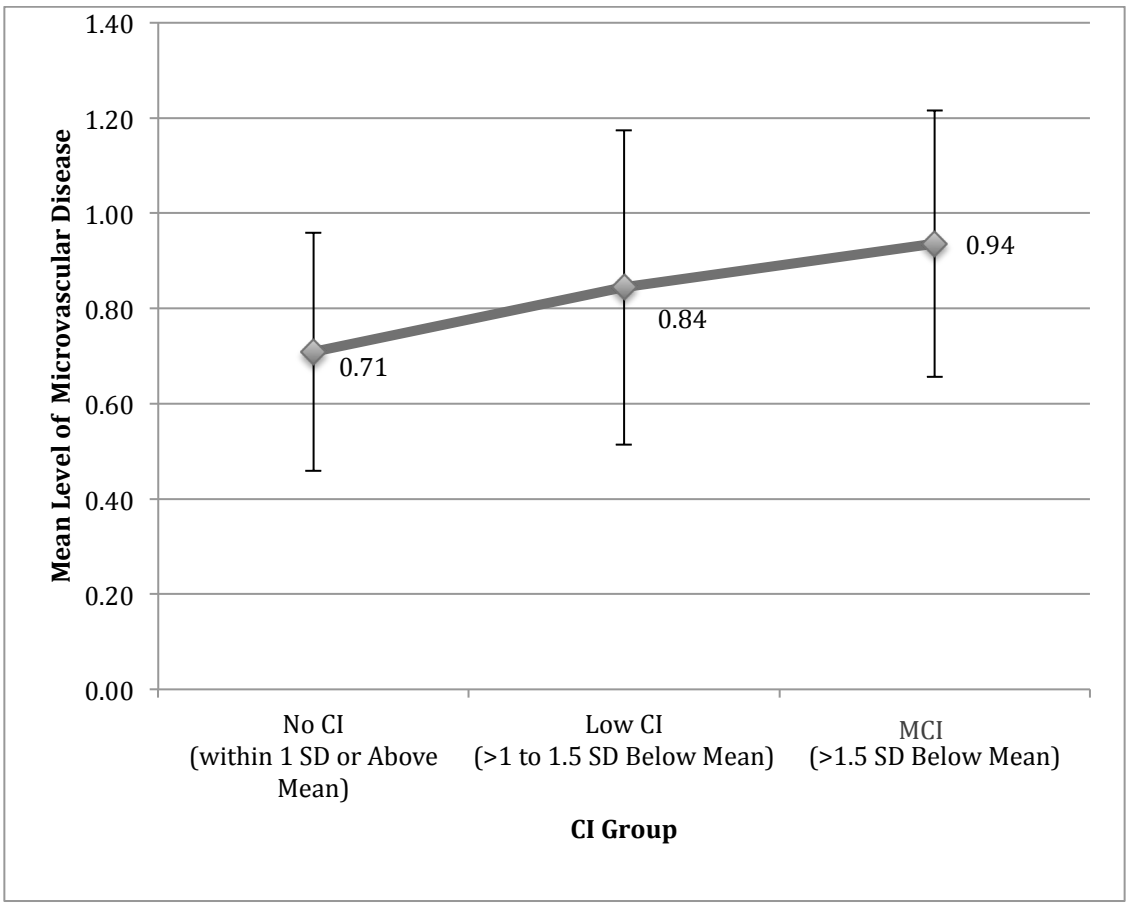

Figure 6.4. Microvascular disease by cognitive impairment (CI) group.

Higher microvascular disease is correlated with demographic factors including age (r_s = .310, $p=.002$, two-tailed), education (r_s =

-.227, p =.028, two-tailed), as well as diabetes health variables including mean HbA1c (r_s = .444, p=.000, two-tailed), and insulin resistance (r_s = -.340, p=.001, two-tailed), as well as indicators of diabetes burden including duration of diagnosis (r_s = .405, p=.000, two-tailed), and a trend towards a relationship with general intelligence (r_s = -.199, p =.055, two-tailed) and age of onset (r_s = -.190, p=.067, two-tailed). Using ANCOVA, when controlling for each of these factors, the significant relationship between microvascular disease and level of cognitive impairment remained significant. The results of the ANCOVA are displayed in Table 6.10

Table 6.10 *ANCOVA Microvascular Disease and CI Group with Demographic and Diabetes Health Covariates*

	Microvascular Disease by CI Group Controlling for Covariate				
Covariates	No CI Mean (SE)	Low CI Mean (SE)	MCI Mean (SE)	(df) *F*	*p* value
None	.708 (.035)	.844 (.077)	.936 (.055)	(2,90) 6.23	.003*
Age	.713 (.037)	.843 (.062)	.928 (.052)	(2,90) 6.01	.004*
Education	.710 (.038)	.846 (.064)	.931 (.055)	(2,90) 5.84	.004*
General Intelligence	.715 (.039)	.838 (.065)	.926 (.056)	(2,90) 4.73	.011*
Mean HbA1c	.731 (.035)	.843 (.058)	.901 (.050)	(2,89) 4.25	.017*
Insulin Resistance	.721 (.037)	.819 (.062)	.940 (.053)	(2,88) 5.83	.004*
Duration of Diagnosis	.720 (.037)	.862 (.062)	.899 (.053)	(2,90) 4.54	.013*
Age of Onset	.711 (.038)	.851 (.064)	.926 (.055)	(2,90) 5.52	.005*

*$p<.01$ Note. Two variables were transformed to normalize for GLM analysis including Microvascular Disease (square root) and Insulin Resistance (Log).

Together, the results indicate that higher cognitive impairment in this T1DM group is related to higher severity rating of microvascular disease, a common diabetes complication.

Increased severity of microvascular disease is also related to higher systolic blood pressure (r_s =.204, p=.049, two-tailed). ANCOVA indicated that a significant relationship between microvascular disease and cognitive impairment remained when controlling for these indicators of cardiovascular health, including systolic blood pressure, F(2,90)=5.45, p=.006. Controlling for this general health variable did not change or alter the relationship between microvascular disease and cognitive impairment.

Mean HbA1c

Mean HbA1c is also used as a diabetes health variable with lower values, an indication of tighter glucose control, related to fewer diabetes complications including retinopathy. The MCI group was compared to the No CI group on level of mean Hba1c (Low </=7.9%, Midrange 8.0-8.8%, High >8.8%), the same divisions used in the cognitive study.

Mean HbA1c levels were not significantly related to levels of cognitive impairment (r_s = .130, p=.213). Figure 6.5 shows a comparison of the percentage of participants from the MCI (n=25) and No CI (n=50) groups categorized within each mean HbA1c level.

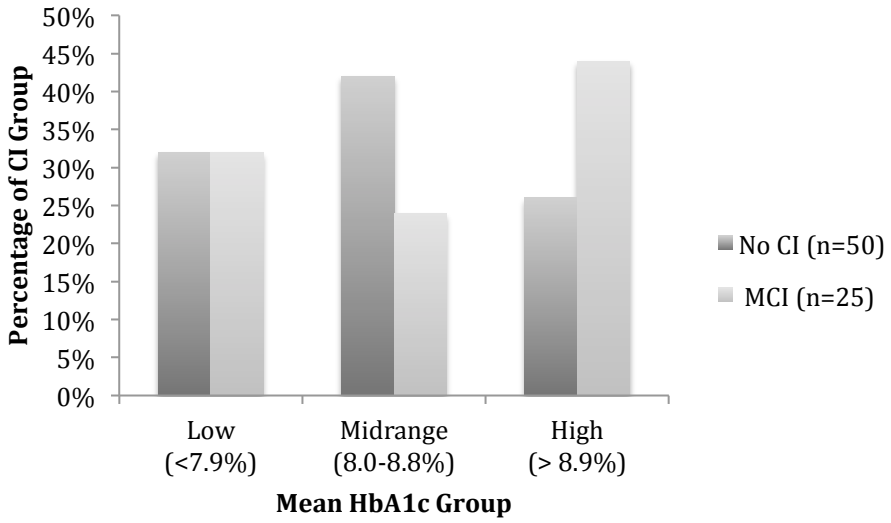

Figure 6.5 Percentage of participants at each mean HbA1c level in the MCI and No CI group

There are 50 instead of 51 participants in the No CI group because mean HbA1c could not be calculated for 1 participant. There was a higher proportion in MCI group (44%) compared to the No CI group (26%) that fell in the highest category of mean HbA1c (mean HbA1c ≥8.9%) showing a trend towards higher levels of blood glucose (i.e. lower glucose control) in this group. However, 32% of both the MCI and No CI groups were classified in the Low HbA1c category. Eighteen percent more of the No CI group (42%) are classified in the Midrange HbA1c group (mean HbA1c 8.0-8.8%) than the MCI group (24%). Most participants in the No CI group are classified in the Low and Midrange HbA1c range (74%) and most of the MCI group (68%) are classified in the Midrange to High HbA1c range. However, results of chi square analysis indicated that there is no significant association between the level of cognitive impairment and level of mean HbA1c, $\chi^2(2)=3.19$,

p=2.03, indicating that there was no difference between the observed and expected frequencies for level of mean HbA1c between the cognitive impairment groups.

Results of ANOVA indicated that the cognitive impairment groups did not differ in mean HbA1c level, F (2,89)=1.54, p=.22, with a small effect size, d=0.2. Planned comparisons indicated only a trend that the MCI group show higher mean HbA1c values than the No CI group, t(90)=-1.76, p=.083, two-tailed, with a medium effect size, d=0.4.

This trend may be better explained by other factors. Mean HbA1c is correlated with total microvascular disease (r_s = .444, p =.000, two-tailed). ANCOVA revealed that when controlling for microvascular disease the relationship between mean HbA1c and CI group is not significant, F(2,89)=.098, p=.91, with a lower F value than for the original ANOVA, F(2,89)=1.54, p=.22. Planned comparisons indicated there was no significant difference between the MCI and No CI groups, t(89)=.369, p=.71 or between the MCI and Low CI group, t(89)=.036, p=.97, after controlling for microvascular disease.

Although there are some results that indicate the MCI group shows higher HbA1c than the group with no cognitive impairment, this association seems to be better explained by other factors such as the increased severity of microvascular complications in those with higher HbA1c.

Severe Hypoglycaemic Events

The occurrence of severe hypoglycaemic events is another indicator

of level of diabetes glucose control. Severe hypoglycaemic events are experiences of extremely low blood glucose, which require another person's assistance for recovery. A greater number of severe events is an indicator of frequent extreme low blood glucose. Although severe hypoglycaemic events have an immediate impact on cognitive function, large studies have not identified this as a risk factor for cognitive impairment in the long-term (Jacobson et al., 2011). The MCI group was compared to the No CI group on average number of severe hypoglycaemic events per year (Low ≤.06 events per year, High >.06 hypoglycaemic events per year), the same divisions of hypoglycaemia used in the cognitive study. The variable was dichotomized as it was not normally distributed with a large range of values.

There was a trend for those with higher cognitive impairment to have a higher average number of hypoglycaemic events per year (r_s=.194, p=.061, two-tailed). The No CI and MCI group were also compared on incidence of hypoglycaemic events. Results of chi square analysis indicates that there is a significant association between level of average hypoglycaemic events per year and the presence of objective cognitive impairment, $\chi^2(1)=4.83, p=.028$. The odds of being in the severe hypo group with MCI is 1.78. The odds of being in the severe hypo group with no CI is 0.59. Based on the odds ratio (1.78/.59=3.02), those in the MCI group are 3 times more likely to experience a higher average of severe hypoglycaemic events per year than those in the No CI group. In this T1DM sample there is a relation between having more frequent severe hypoglycaemic events and higher levels of cognitive

impairment. However, recurrent hypoglycaemia has been generally dismissed as a cause for cognitive deficit in T1DM based on the results of large longitudinal studies (Jacobson et al., 2011).

Insulin Resistance

Although insulin resistance has been debated as a possible factor affecting cognitive function in T1DM and insulin dose (positively related to insulin resistance) was one of the factors related to higher levels of MCI in type 2 diabetes research, there was no significant relationship between level insulin resistance and level of cognitive impairment, r_s = -.061, p=.56, two-tailed in this study sample. ANOVA comparison revealed no significant differences between CI groups in level of insulin resistance, $F(2,89)$=.946, p=.39, with a small effect size, d=0.2. Insulin resistance is not revealed as an important factor in relation to cognitive impairment in this T1DM sample.

Duration of Diagnosis

Higher cognitive impairment was also correlated with longer duration of diagnosis, r_s=.210, p=.042, two-tailed, an indicator of greater disease burden. ANOVA results indicate a significant difference between groups with varying levels of cognitive impairment for duration of diagnosis $F(2,91)$ = 3.45, p=.036, with a small effect size, d=0.3, shown in Figure 6.6

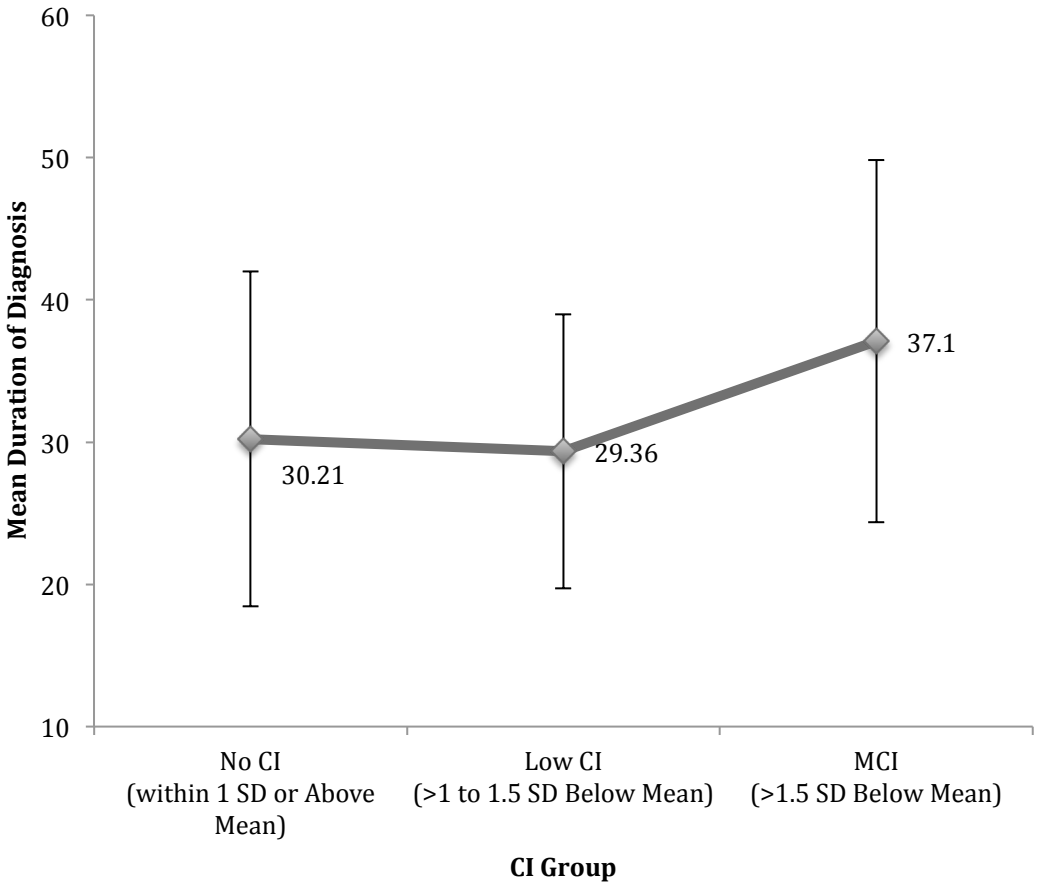

Figure 6.6. Mean duration of diagnosis by cognitive impairment (CI) group.

Planned comparisons indicate that the MCI group showed longer mean duration of diabetes than the No CI group, $t(91) = -2.42$, $p=.018$ (two-tailed), $d=0.5$ and the Low CI group, $t(91) = -2.15$, $p=.035$ (two-tailed), $d=0.5$. These results indicate that those with the highest level of cognitive impairment in the study group have been diagnosed with diabetes for longer than those with no or low levels of objective cognitive impairment.

Having diabetes longer also means that these participants are likely older, and have more severe complications, factors that may also

increase the likelihood of higher cognitive impairment. It may be that one of these factors is actually the reason for the difference between the MCI and Low CI groups. Given that duration of diagnosis is significantly correlated with participant age (r=.448, p=.000, two-tailed), and microvascular disease (r_s=.405, p =.000), it could be that the difference in duration of diagnosis between the groups is due to one of these factors. Using ANCOVA, when controlling for participant age, there was still a significant difference between CI groups on duration of diagnosis, $F(2,90)= 3.5$, p=.034.

Spearman's rho correlation indicated that longer duration of diabetes is associated with indicators of cardiovascular health, lower diastolic blood (r_s = -.396, p=.000, two-tailed), and lower blood pressure (r_s = -.205, p=.047, two-tailed). ANCOVA results indicate the relationship between MCI and duration of diagnosis remains when controlling for indicators of cardiovascular health, including diastolic blood pressure, F (2,90)=3.76, p=.027 and incidence of high blood pressure, $F(2,90)=3.83$, p=.025.

The people with diabetes longer also had a higher severity of microvascular disease. Results of the ANCOVA indicates that when controlling for microvascular disease, the difference between groups on duration of diagnosis becomes insignificant, $F(2,90)= 1.87$, p=.16 This suggests that the relationship between longer duration of diagnosis and greater cognitive impairment may be explained by a higher level microvascular disease.

Mean HbA1c is not correlated with duration of diagnosis in the study sample (r_s=-.001, p=.99), however is a variable of interest in this study. Results of the ANCOVA indicated that the significant difference between MCI groups based on duration of diabetes remains when controlling for mean HbA1c, $F(2,89)$= 3.18, p=.046.

Results indicate that longer duration of diagnosis is related to higher levels of cognitive impairment, however this may be explained by greater incidence of microvascular disease in this group.

Age of Onset

Although the omnibus F indicated no significant difference between cognitive impairment groups based on age of diabetes onset, $F(2,91)$ = 2.78, p=.068, with a small effect size, d=0.3, there was a trend towards a difference. Planned comparisons indicate that the MCI group were diagnosed with diabetes at a younger age than the No CI group, $t(91)$= 2.05, p=.043, d=0.5 and the Low CI group, $t(91)$= 2.06, p<.042, d=0.5 shown in Figure 6.7.

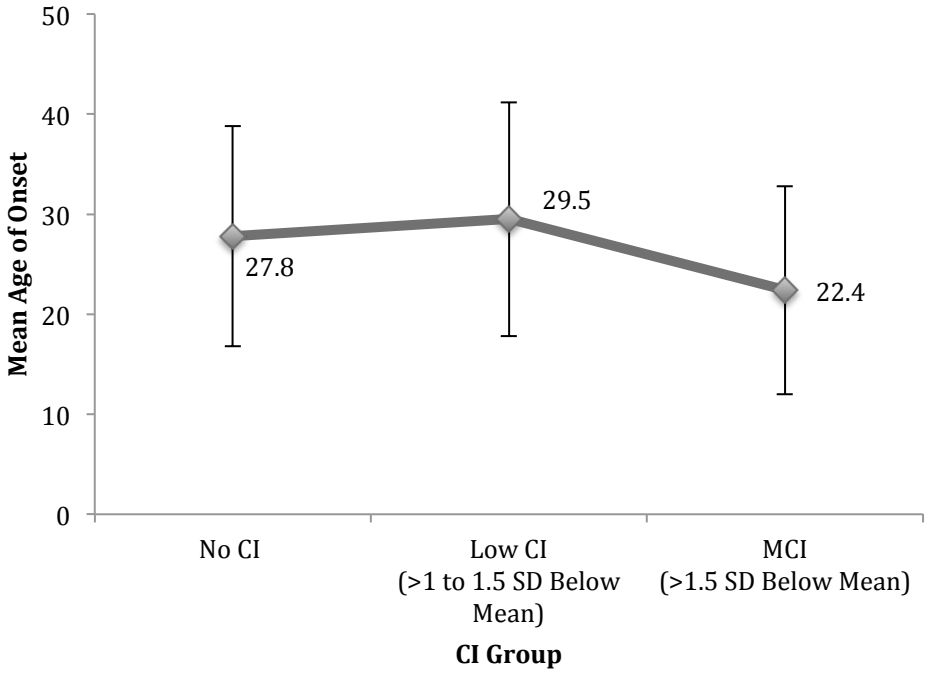

Figure 6.7 Mean age of onset by cognitive impairment (CI) group.

Age of onset is an indicator of greater disease burden related to duration of diagnosis, and possibly increased risk of microvascular complications. Although age of onset is highly correlated with duration of diagnosis (r =-.715, p<.000, two-tailed), it may measure factors that are somewhat different because age of onset it is not significantly correlated with microvascular disease (r_s=-.190, p=.067). Younger age of diabetes onset is correlated with younger participant age in this sample (r=.305, p=.003). If those with early onset of diabetes tend to be younger it is not likely that age is a factor in the differences in age of onset between the MCI and Low CI groups. Using ANCOVA, when controlling for participant age, the associated F value for CI group becomes significant, $F(2,90)$= 3.51, p=.034. This suggests that there is a significantly lower age of onset in the highest cognitive impairment

group than for groups with lower levels of cognitive impairment when participant age is taken into consideration.

ANCOVA results indicated that when controlling for microvascular disease, there is no significant difference between age of onset for CI groups, $F(2,90)=2.14$, $p=.124$. Similarly, the difference in age of onset between the MCI and Low CI groups is not significant when controlling for mean HbA1c, $F(2,89)=2.8$, $p=.066$. The fact that the relationship between age of onset and cognitive impairment level is attenuated with the addition of these diabetes health variables suggests that these indicators of poor diabetes health might better explain this relationship.

What are the main predictors of MCI identification?

Finally, diabetes factors with a significant relationship to CI group were entered into a multiple regression analysis to determine which factors were best at predicting MCI group versus Low/No CI group membership. Using backward stepwise entry with an exclusion criteria of $p<.055$, Logistic regression was used to examine which factor or group of factors was most predictive of MCI group membership. The following factors were entered: Age, NART-IQ (crystallized IQ), microvascular disease, long-term HbA1c, duration of diagnosis, the dichotomized variable severe hypoglycaemic events. Given the aim to explore signs of accelerated ageing, participant age was also included. Duration of diagnosis was chosen over age of onset (which are highly correlated, $r=-.715$, $p=.000$, two-sided), as it had a slightly higher effect size when

comparing CI groups to prevent multicollinearity of variables in the analysis. The results of the final step of logistic regression are displayed in Table 6.11. The results indicate that the best predictors of MCI group membership were greater microvascular disease (effect size *r*=.42), and lower crystallized IQ score (effect size *r*=.40), retained as significant predictors in the final step of the regression model. Together the final model explained 36% of the variance in membership in the MCI group. The final model predicted CI group membership with 78.9% accuracy.

Table 6.11 *Results of backwards stepwise logistic regression for predicting MCI group membership*

Step	Predictors	*B (SE)*	Wald	exp *b*	*p*	χ^2	R^2
1	Constant, Age, IQ, Duration, Micro, Hypo (2)				<.001	26.01 (df=5)	.40
2	Constant, IQ, Duration, Micro, Hypo (2)				<.001	26.01 (df=4)	.40
3	Constant, IQ, Micro, Hypo (2)				<.001	24.14 (df=3)	.38
4	Constant, Micro, IQ				<.001	22.58 (df=2)	.36
	Constant	-6.839 (1.66)	17.06		<.001		
	Micro	3.698 (1.26)	8.67	40.363	.003		
	IQ	.947 (.335)	7.97	2.577	.005		

Note: Predictors and Model coefficients are provided for each step. Beta values for each variable are provided for the last step.
Nagelkerke R^2 reported
Micro: Microvascular Disease (Sqrt transformed)
IQ: NART IQ (Reverse Sqrt transformed)
Hypo (2): Dichotomized hypoglycaemic events (≤.06/year or >.06/year)

The analysis was run again with only participants under 65, leaving n=41 in the No CI group and n=21 in the MCI group. Results are displayed in Table 6.12. The findings were consistent with the results of the first analysis. The best predictors of MCI group membership were

greater microvascular disease (r=.30), and lower crystallized IQ score (r=.20), retained as significant predictors in the final step of the regression model (Table 4). Together the final model explained 41% of the variance in membership in the MCI group. The final model predicted CI group membership with 80.6% accuracy.

Table 6.12 *Results of Backwards Stepwise Logistic Regression For Predicting MCI Group Membership For Participants Under Age 65*

Step	Predictors	*B (SE)*	Wald	exp *b*	*p*	χ^2	R^2
1	Constant, Age, IQ, Duration, Micro, Hypo(2)				<.001	24.60 (df=5)	.45
2	Constant, IQ, Duration, Micro, Hypo(2)				<.001	24.12 (df=4)	.45
3	Constant, IQ, Micro, Hypo(2)				<.001	22.95 (df=3)	.43
4	Constant, Micro, IQ				<.001	21.43 (df=2)	.41
	Constant	-7.181 (1.91)	14.097		<.001		
	Micro	4.378 (1.53)	8.238	79.71	.004		
	IQ	.907 (.402)	5.102	2.48	.024		

Note: Predictors and Model coefficients are provided for each step. Beta values for each variable are provided for the last step.

Nagelkerke R^2reported

Micro: Microvascular Disease (Sqrt transformed)

IQ: NART IQ (Reverse Sqrt transformed)

Hypo (2): Dichotomized hypoglycaemic events (≤.06/year or >.06/year)

6.6. Discussion

6.6.1. Question 1

What is the incidence and nature of MCI in the study sample? How does this compare to the incidence of MCI reported in research of the general population?

Despite the fact that most of the study group was middle-aged, the incidence of MCI is relatively high (27%). Population studies have shown MCI incidence of up to 20% in people over the age of 65 (2011). This suggests a possibility that a higher percentage of people may be classified with MCI in T1DM groups at a relatively younger age than in studies of the general population over the age of 65. The high incidence of MCI in this primarily middle-age group (mean 58.7) suggests that there are early signs of cognitive ageing in this group.

The nature of cognitive impairment in the group with MCI was primarily in the domains of executive function and processing speed. A particular deficit in processing speed has been found in those with MCI in the general diabetes population (Arvanitakis et al., 2004; Toro et al., 2009). Performance on delayed recall and executive function tests have also been related to progression to dementia (Gauthier et al., 2006). The risk of dementia has been studied in the general diabetes population, which is composed primarily of those with type 2 diabetes (Biessels et al., 2006; Bruce, Harrington, Davis, Davis, & Fremantle, 2001). There is a higher incidence of vascular dementia than

Alzheimer's disease for those with primarily T2DM (Biessels et al., 2006), although both are elevated in relation to the general population. The incidence of dementia in groups with T1DM has not been specifically examined. Indications in this study of a high risk of MCI in this group, suggest the need to examine this group more closely in this respect.

6.6.2. Question 2

Are there differences in the age, education or general intelligence of the participants in the study sample who show MCI in comparison to those who show lower levels of objective cognitive impairment?

Results showed that the group with MCI was the same age as those with lower levels or no cognitive impairment and most were under the age of 65. Although those with MCI did show lower premorbid IQ however, this was in the upper average range and not likely to impact cognitive processing. That the average IQ in the MCI group was high highlights the general strong general intelligence within in the study group and suggests that this group should not be particularly vulnerable to early MCI. The cognitive impairment focused on the middle-aged adults in the group highlights the relatively early cognitive impairment in the T1DM group compared to those in the general population. Early incidence of MCI contributes to evidence of an early cognitive ageing process in this group.

6.6.3. Question 3.

Are there differences in general health variables and health habits in those who show MCI in comparison to those who show lower levels of objective cognitive impairment?

Regarding health habits, cognitive impairment was related to lower level of self-reported daily cognitive activity even when age, IQ and education were taken into account. However, this could be a result or cause of cognitive impairment. Those with lower cognitive activity may be more vulnerable to cognitive impairment or those with cognitive impairment may engage in less daily cognitive activity. Although the direction of the relationship is uncertain, recommendations for engaging in cognitive activity may benefit in prevention of MCI in this group.

There were no general health variables that could better explain the relationships between microvascular disease and diabetes duration with cognitive impairment, even though these were correlated with measures of cardiovascular health including systolic and diastolic blood pressure. As most of this older T1DM group had hypertension (84%) with 78% on blood pressure medication, it may be difficult to determine if there is an effect of cardiovascular health on cognitive impairment in this sample as found in the results of the cognitive study.

6.6.4. Question 4.

Are there differences in diabetes health variables for those who show MCI in comparison to those who show lower levels of objective

cognitive impairment? What are the main predictors of MCI identification?

Results suggest that there is a relationship between the incidence of MCI in the study sample and indicators of sub-optimal diabetes control. The group with MCI had more severe microvascular disease (d=0.76), were 3 times more likely to experience a higher average of severe hypoglycaemic events per year, longer diabetes duration (d=0.5) and younger age of onset (d=0.5) than the group with no cognitive impairment. The finding that those with higher cognitive impairment also experience more frequent severe hypoglycaemic events further highlight this may be a particular vulnerability for older adults. It may also be that those with microvascular disease are more vulnerable to the effects of recurrent severe hypoglycaemic events. A final regression analysis retained only one diabetes health variable as predictive of high cognitive impairment including, higher severity of microvascular disease along with a measure of general cognitive intelligence, NART IQ. These results highlight the importance of blood glucose control within an optimal range to both limit microvascular disease, and prevent exposure to recurrent severe hypoglycaemic events. Limiting these complications may help in limiting early cognitive impairment for those with T1DM.

6.6.5. Conclusions

What do the results tell us about cognitive ageing in T1DM and its relationship with theories of cognitive ageing?

The risk of MCI has not been previously identified in groups with T1DM. Results suggest that middle-aged adults with T1DM may be at higher risk for MCI, just as those with T2DM. Park & Reuter-Lorenz (2009) suggest an early need for scaffolding with some chronic diseases. The need for early scaffolding is expected in T1DM, as there is evidence of early structural brain differences in this group (Perantie et al., 2007). Park and Reuter-Lorenz (2009) suggest early use of scaffolding leads to more vulnerability to accelerated ageing and higher levels of cognitive impairment. It was clear that those individuals with greater indication of vascular disease, greater severity of microvascular disease, were at most risk of MCI. This may initiate an early need for scaffolding processes in these individuals to offset impacts on the brain. The identification of MCI in this primarily middle-aged group provides evidence of early cognitive ageing in this group. In Chapter 8, the brain functioning of those with retinopathy will be directly compared to investigate evidence that this scaffolding process may be occurring at an earlier stage for those with high severity retinopathy.

The STAC theory (Park& Reuter-Lorenz, 2009) highlights activities that would promote "scaffolding enhancement" include new learning, engagement, exercise and cognitive activity. The cognitive reserve theory suggests a higher level of reserve for those engaged in these lifestyle-enhancing activities (Stern, 2002; 2006). The correlation with increased cognitive activity and lower cognitive impairment suggests a potential route for prevention of cognitive impairment in

this group. Engagement in these activities is enhanced through psychological wellbeing. The influence of psychological variables on diabetes control and cognitive function will be explored in Chapter 7.

Chapter 7
The Influence Of Personal and Psychological Variables on Diabetes Health Variables and Cognitive Function

7.1. Introduction

Results of the cognitive study highlighted that severity of microvascular disease was the strongest predictor of cognitive function and MCI in the study group. As well results highlighted personal health habits (cognitive activity, exercise) that could be of potential benefit in the treatment of those with T1DM for maintenance of optimal cognitive function in ageing. There are a number of psychological variables that can support adherence to treatment or healthy lifestyle choices. Psychological variables could influence the relationship between T1DM and cognition through influence on self-management and glycaemic control. These factors could potentially support maintenance of cognitive function in ageing for individuals with T1DM. For example, diagnosis of clinical depression has been related to reductions in scores on cognitive tasks demanding high processing resources (specifically processing speed and working memory tasks) for both younger and older populations (Tsourtos, Thompson, & Stough, 2002; Nebes et al., 2000). These modifiable factors may potentially work together with the scaffolding process (Park & Reuter-Lorenz, 2009) and minimize the effects of disease and ageing on cognitive function or increase overall level of cognitive reserve (Stern, 2002; 2006).

7.2. Study Questions

1. What percentage of the study group rate clinical symptoms of anxiety and depression? How does this compare to the incidence in the general population?
2. Do measures of well being relate to demographic variables?
3. Do measures of well-being relate to diabetes health variables?
4. Do measures of well being relate to cognitive function?

7.3. Materials and Method

Standardized questionnaires were administered to participants before completing the cognitive assessments to investigate various psychological variables potentially important in optimal cognitive function, glycaemic control and minimizing diabetes complications. These include depression, anxiety and well being. Each participant completed the following questionnaires either on their own or with the chief investigator.

1. Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). This is a measure of anxiety and depressive symptoms experienced. Participants are asked to rate how they have been feeling over the past week on a 14-item scale with 7 items about depression (HADS D) and 7 about anxiety (HADS A). Higher scores indicate higher psychological distress. Scores below from 0 to 7 are considered normal, 8-10 mild, and 11 and more moderate to severe and probable cases of mood disorder.

2. Well-Being Questionnaire–28 (WBQ: Bradley, 1994). This questionnaire includes questions regarding positive and negative well being, energy and stress, and attitudes related to diabetes. This measure was specifically developed for evaluation of individuals with diabetes. This is not a norm-referenced measure, but designed for tracking patient changes over time.

7.4. Statistical Analysis

Spearman's rho and Pearson's correlation were used in a correlation analysis to examine the relationship between ratings of anxiety, depression, general and diabetes well-being with diabetes health variables and cognitive test scores. Chi square was used to look at group composition based on retinopathy level. ANOVA was used to further explore relationships highlighted in the correlation analysis. Multiple regression was used to determine significant predictors of well-being and cognitive function.

7.5. Results

7.5.1. Question 1

What percentage of the study group rate clinical symptoms of anxiety and depression? How does this compare to the incidence in the general population?

Ratings from the Hospital Anxiety and Depression scale (HADS) indicate that just under a quarter of participants rated above normal symptoms for HADS A (23.4%) and much less for the HADS D

(10.6%). Of these participants, only a small percentage showed probable clinical levels (moderate or severe) of anxiety or depression (HADS score ≥ 11), displayed in Table 7.1. Anxiety ratings indicated just over 8% showed ratings of moderate anxiety (HADS score 11-14) and only 3% showed ratings of severe anxiety (HADS score 15-21). Over three quarters of participants had ratings within the normal range (HADS score 0-7) for anxiety with fewer than 12% of participants reported mild values for anxiety (HADS score 8-10). Depression ratings indicate that only 2 participants rated high levels of depression, and both were at the moderate level. The majority of people in the study sample, about 90%, rated themselves to have normal values for depression with just over 8% rated themselves to be in the mild range.

Table 7.1 *Percentage of Participants within Categories for HADS Anxiety and Depression Ratings*

	HADS Anxiety			HADS Depression	
Category (Score Range)	n	%		n	%
Normal (≤ 7)	72	76.6		84	89.4
Mild (8-10)	11	11.7		8	8.5
Moderate (11-14)	8	8.5		2	2.1
Severe (≥ 15)	3	3.2		0	0
Total	94	100		94	100

Participants received average ratings overall on HADS A and HADS D. The mean anxiety rating for the study sample was within the

normal range ($\bar{x}$=4.99, SD = 4.3) with a range from 0 to 17. The mean anxiety rating was slightly higher and showed higher variability than the mean rating for depression ($\bar{x}$=3.41, SD = 2.8) with a range from 0 to 11.

The present study included a self-selected sample, who was not formally identified with psychological disorders, although some (14.9%) participants were currently or recently using medication for depression (14/94), none were taking anti-anxiety medication. The mean for anxiety was not significantly higher (t (92)=-1.58, p=.12) for those taking anti-depressants ($\bar{x}$=6.64, SD = 4.63) compared to those who did not take this medication ($\bar{x}$=4.7, SD = 2.8). The range of anxiety scores was narrower for those who were taking anti-depressants (0-14) than for those who were not taking this medication (0-17). The mean depression score was significantly higher (t (92)=-2.40, p<.05) for those taking anti-depressants ($\bar{x}$=5.07, SD = 2.97) compared to those who do not take this medication ($\bar{x}$=3.13, SD = 2.77). The range of depression scores was narrower for those who were taking anti-depressants (1-10) and only included those in the normal and mild range, compared to those who were not taking this medication (0-11), including the 2 participants in the moderate range.

To determine whether there are any patterns in the items typically endorsed by participants in this T1DM group, an item analysis was undertaken. Results are displayed in Figure 7.1. Most of the group endorsed items relating to positive well being. Over 60% of participants gave scores of 0 for items relating to humor, cheer and

enjoyment in relaxing activities (a score of 0 indicates the participant does not have any problem in the area). The negatively endorsed items may relate to physical health of the group. There were two items in particular that elicited scores of 1 or more (showing some level of difficulty) for the majority of the study sample participants including, "I feel slowed down" and "I still enjoy the things I used to enjoy". It appears that ratings are related to physical limitations of middle-aged and older adults with T1DM. Over one quarter of participants endorsed scores over 1 indicating problems occurred very often or all the time for the item "I feel slowed down". This is also reflected in participants' responses to the Well-Being Questionnaire (WBQ). On the WBQ Energy Scale, most participants indicated some issues with energy only sometimes feeling "energetic, active, and vigorous" (49%), sometimes feeling sluggish (55%), and sometimes feeling tired (44%). Results of Spearman's Rho correlation indicated that there was a high negative correlation between HADS depression scores and the WBQ general energy (r_s=-.645, p<.01).

Results on the WBQ General Negative Well-Being Scale reinforced that high scores of depression in the study group were not derived from items relating to high psychological distress. Most participants did not endorse having "crying spells or feeling like it" (62%), and 44% indicated that they did not feel "down hearted and blue" at all and 40% indicated that they sometimes felt this way over the past week. Although it may be assumed that managing diabetes may relate to greater negative feelings, symptoms of depression did not appear to be

related to dealing with diabetes for most. On the WBQ Diabetes Negative Well-Being Scale with only 36% endorsing scores over 0 for "talking or thinking about my diabetes gets me upset or feeling downhearted" and only 35% endorsed scores over 0 for "because of my diabetes I get depressed".

Turning to anxiety, items endorsed did not represent high psychological distress. Items endorsed by the study group on the HADS A scale are shown in Figure 7.2, the majority of participants report scores of 1 or more on most items relating to general worries and tension. Reported anxiety is related to general worries and tension rather than attacks of anxiety. Participants endorsed a score of 1 for sometimes feeling "tense or wound up" (46%), sometimes "worrying thoughts go through my mind" (34%), have some difficulty "sitting and feeling relaxed" (43%), sometimes get a frightened feeling like butterflies in the stomach" (41%), and sometimes "feel restless as if I have to be on the move" (35%). Most participants did not endorse items concerning anxiety attacks without a known cause including, "I get a sort of frightened feeling as if something awful is about to happen" (60% -not at all), "I get sudden feelings of panic" (66% - not at all) or having frightened feelings like butterflies in the stomach (52% -not at all). Participants endorsed scores over 1 regarding "feeling restless as if I have to be on the move" (28%). Only a few endorsed scores over 1 for having a "frightened feeling like butterflies in the stomach" (7%) or having "sudden feelings of panic" (12%). This was also reflected in participants' responses on the WBQ on the

General Negative Well-Being Scale. Most indicated that they did not "feel afraid for no reason at all" (78%) and did not "get upset easily or feel panicky" (58%). In contrast on the WBQ Diabetes Negative Well-Being, most endorsed feeling some "worry about the management of my diabetes" (70%), and indicated endorsement of the item "because of my diabetes I worry about the future (63%).

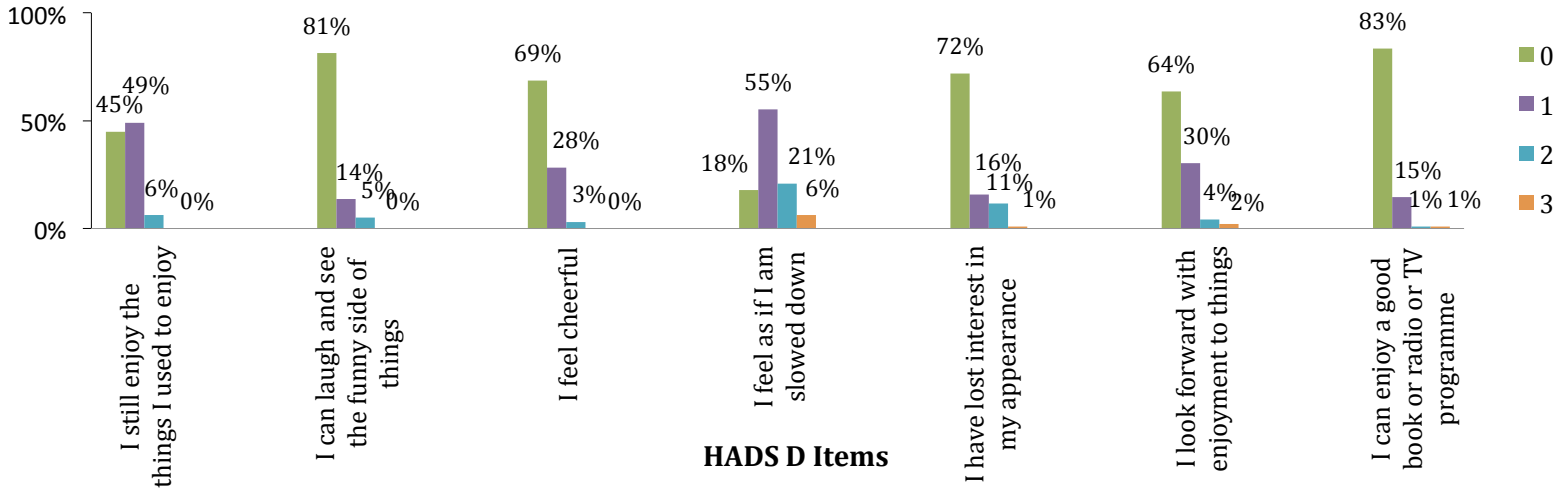

Figure 7.1 Percentage of participants' endorsement of scores (0-3) on HADS D items.

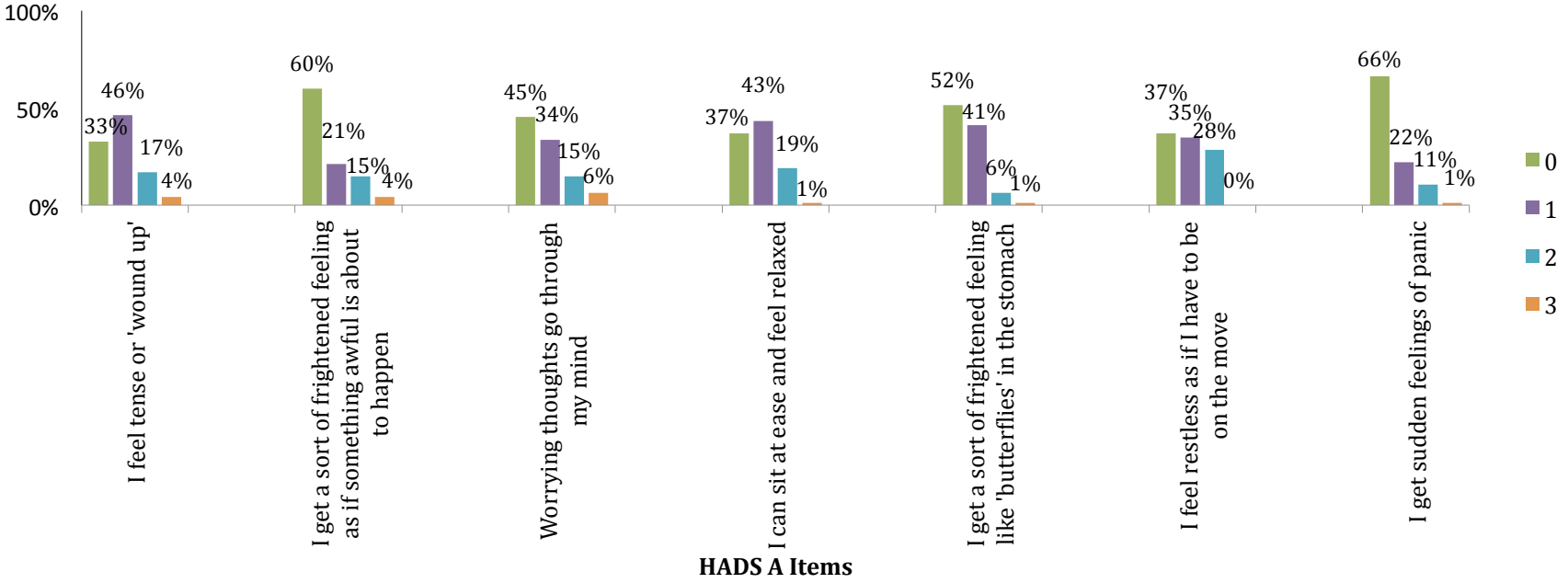

Figure 7.2 Percentage of participants' endorsement of scores (0-3) on HADS A

How does the incidence of anxiety and depression in the study sample compare to the incidence in the general population?

In the study sample, a greater percentage of the group gave normal ratings of anxiety (76.6%) and depression (89.4%) symptoms in comparison to a UK normative study (Crawford et al., 2001). In the UK population study, normal ratings of anxiety were attained by a smaller percentage of participants (66.6%) with a higher number classified in the mild range of problems with anxiety (20%) than in the study sample (11.7%). In the UK normative sample (Crawford et al., 2001). the mean anxiety rating of the population ($\bar{x}$=6.14, SD=3.76) was slightly higher than that of the study sample ($\bar{x}$=4.99, SD = 4.3) and the mean depression rating ($\bar{x}$=3.68, SD=3.0) in the UK sample was similar to that of the study sample ($\bar{x}$=3.41, SD = 2.8). The rates of probable clinical disorders of anxiety and depression are also slightly lower than the rates found in normative studies. The rate of moderate and severe anxiety in the UK population sample (Crawford et al., 2001) was 12.6% (11.7% in the study sample) and depression was 3.6% (2.1% in the study sample).

7.5.2. Question 2

Do measures of well being relate to demographic variables?

Spearman's rho correlation coefficient was used to explore the relationships between well-being and diabetes health. Full correlation tables are provided in Appendix P. Correlations of interest are highlighted in text.

Age

Participant age was consistently correlated with measures of well being across measures with the exception of diabetes stress and HADS depression (Table 7.2). One-tailed correlation was used for this exploratory analysis.

Table 7.2 *Correlation Between Ratings of Well-Being and Participant Age*

Variable	Age
HADS-Anxiety	-.289 (.002)**
HADS-Depression	-.143 (.09)
WBQ General Negative Well-Being	-.327 (.001)**
WBQ General Energy	.302 (.001)**
WBQ General Positive Well-Being	.304 (.001)**
WBQ General Stress	-.393 (.000)**
WBQ Diabetes Negative Well-Being	-.243 (.009)**
WBQ Diabetes Stress	-.129 (.11)
WBQ Diabetes Positive Well-Being	.239 (.010)*
WBQ General Well-Being	.406 (.000)**
WBQ Diabetes Well-Being	.264 (.005)**

Spearman's rho, one-tailed correlation values, *p<.05, **p<.01

Middle-aged and older adults appear to have a positive outlook in general. Specifically, measures of positive well-being on the WBQ (general energy, general positive well-being, general well-being, diabetes positive well-being and diabetes well-being) were related to

older age. Measures of anxiety and negative well-being (HADS A, diabetes negative well-being, general stress, general negative well-being) were related to younger age.

Education

Of the demographic variables, education has a positive relationship with WBQ general positive well-being (r_s =.215, p =.019), with higher education related to higher ratings of positive well-being. This relationship was strengthened when controlling for participant age (pr_s =.252, p <.01).

Gender

Is there a difference between ratings of well-being for women and men as in previous studies? There are a near equal number of females (n=49) and males (n=45) in the study sample. Female gender was related to higher ratings on the WBQ general negative well being (r_s =-.265, p=.005) and diabetes negative well-being (r_s =-.180, p<.05). There was no significant relationship between female gender and ratings of depression, HADS D (r_s =-.077, p=.23) or anxiety, HADS A (r_s =-.154, p=.07). Because of low numbers of participants who rated themselves to have above normal (Mild/Moderate/Severe) ratings on the HADS, ratings were recoded into low normal (score=0-3), high normal (score=4-7) and above normal (score=8 and above). A chi square analysis appears to reflect that there is a higher than expected percentage of women that rate themselves in the above normal range on the HADS A scale and fewer than expected men that

rated themselves above the norm ($\chi^2(2)=7.3$, $p<.05$). The numbers and percentages of men and women in each HADS category are presented in

Table 7.3.

Table 7.3 *Percentages of Men and Women in Each Category on the HADS Anxiety Scale*

		HADS A Category			
		Low Normal (Score = 0-3) n (%)	High Normal (Score = 4-7) n (%)	Above Normal (Score = 8+) n (%)	Total n (%)
Female	Count	19	13	17	49
	Exp	21.9	15.6	11.5	49
	% Gender	38.8	26.5	34.7	100
	% HADS	45.2	43.3	77.3	52.1
Male	Count	23	17	5	45
	Exp	20.1	14.4	10.5	45
	% Gender	51.1	37.8	11.1	100
	% HADS	54.8	56.7	22.7	47.9

Exp=Expected Frequency; HADS=Hospital Anxiety and Depression Scale

7.5.3. Question 3

Do measures of well being relate to diabetes health variables*?*

Spearman's rho correlation, partial correlation and multiple regression were used to explore the relationships between diabetes health variables and psychological well being.

Duration and Onset

Those with diabetes for longer had a more positive outlook. Some measures of positive well-being related to duration and age of onset. Longer duration was related to higher diabetes positive well-being (r_s=.253, p=.007). This relationship remained when controlling for age (pr_s=.180, p<.05). Older age of onset was related to higher feelings of general energy (r_s=.174, p=.047) and general well-being (r_s=.199, p=.03); however, these relationships were not significant when controlling for age for either general energy (pr_s=.101, p=.34) or general well-being (pr_s=.102, p=.34). Those with younger age of onset showed higher general negative well-being (r_s=-.176, p<.05), and greater general stress (r_s-.249, p<.01), however these relationships were not significant when controlling for age for either general negative well-being (pr_s=-.096, p=.36) or general stress (pr_s=-.161, p=.12).

Glycaemic Control

Does well-being relate to better outcomes on glycaemic control? Results showed that higher long-term (mean HbA1c) values related to higher scores on the HADS D (r_s=.187, p=.036), greater diabetes stress (r_s=.222, p=.016), and lower diabetes well-being (r_s=-.174, p=.048). These relationships remained when controlling for age; HADS D (pr_s=.205, p<.05), diabetes stress (pr_s=.238, p<.05), and diabetes well being (pr_s=-.208, p<.05).

Higher recent HbA1c (5 year mean) was related to lower diabetes positive well-being (r_s=.182, p=.039), lower diabetes well-being

(r_s=.204, p<.05), and higher diabetes stress (r_s=.181, p=.040). These relationships remained when controlling for age: diabetes positive well-being (pr_s=-.195, p<.05), diabetes well-being (pr_s=-.219, p<.05), and diabetes stress (pr_s=.186, p<.05). Higher current values of HbA1c were particularly associated with lower diabetes positive well-being (r_s=-.176, p=.045). This relationship remained when controlling for age (pr_s=-.179, p<.05).

Results of Kruskal-Wallis (Table 7.4) analysis indicated that when participants were divided into groups based on mean, recent, and current HbA1c, although there was a linear pattern for HADS D scores between groups (low HbA1c group lowest HADS D scores compared to the high HbA1c group), there was no significant difference between the HADS scores for each group. It was also observed that for those with low HbA1c, the HADS D mean rank was numerically higher for groups with more recent HbA1c, whereas for both the Midrange and High HbA1c groups, the HADS D mean rank was numerically lower for groups with more recent HbA1c. This suggests the question of whether mood may be more closely related to mean HbA1c for those with tight control.

Table 7.4 *Kruskal-Wallis comparison of HADS D scores for Mean, Recent and Current HbA1c groups.*

	HbA1c Group				
	Low HbA1c ≤7.9%	Midrange HbA1c 8.0-8.8%	High HbA1c ≥8.9%	*H*	*p*
Mean HbA1c (n)	n=29	n=34	n=30		
HADS D Mean Rank	39.29	48.22	53.07	4.02	0.13
Mdn (SD)	2.0 (2.6)	3.0 (2.7)	3.0 (3.2)		
Recent HbA1c (n)	n=33	n=33	n=28		
HADS D Mean Rank	43.30	47.82	52.07	1.03	0.36
Mdn (SD)	2.0 (2.9)	3.0 (2.3)	3.0 (3.4)		
Current HbA1c (n)	n=32	n=37	n=25		
HADS D Mean Rank	45.63	46.11	51.96	1.60	0.45
Mdn (SD)	3.0 (2.9)	2.0 (2.8)	3.0 (3.1)		

Multiple regression, using backwards stepwise entry, was used to investigate significant predictors of HADS D scores (Table 7.5). Age, retinopathy level, and mean HbA1c were entered into the analysis. In the final step of the model, mean HbA1c was retained as the sole significant predictor of HADS D scores, with a non-significant trend for retinopathy level to have a significant added influence on HADS D scores, $F(2,90)=3.725$, $p<.05$.

Table 7.5 *Multiple Regression Results: Significance of Age, Mean HbA1c and Retinopathy as Predictors of HADS Depression Score*

	B	*SE B*	ß	*t*	*p*
Step 1					
Constant	-.476	3.388		-.140	
Age	-.043	.034	-.131	-1.243	.22
Retinopathy Level	-1.026	.658	-.176	-1.560	.12
Mean HbA1c	.828	.337	.267	2.460	.016*
Step 2					
Constant	-2.950	2.750		-1.073	.29
Retinopathy Level	-1.248	.635	-.214	-1.966	.052
Mean HbA1c	.839	.338	.271	2.486	.015*

Analysis uses multiple regression with backwards stepwise entry
R^2=.092 for Step 1; Δ R^2=-.016 for Step 2 (ps=.22);, *p<.05

Insulin Resistance

A negative relationship was identified between anxiety and insulin resistance. Lower insulin resistance (i.e., higher estimated glucose disposal rate) was related to higher HADS anxiety scores (r_s=.280, p=.003), higher general negative well-being (r_s=.267, p=.005) and higher feeling of general stress (r_s=.183, p=.040). Female gender and age are both related to higher anxiety. The relationship with anxiety remained when controlling for female gender, HADS A (pr_s=.237, p<.05) and when controlling for age (pr_s=.282, p<.01); however, the relationship became non-significant for general negative well-being (pr_s=.146, p=.08) and general stress (pr_s=.121, p=.13). It could be that one or more of the factors used in the calculation of eGDR are

influencing the relationship with HADS A. These include waist-hip ratio (WHR) and current HbA1c. These factors have a relationship in a negative direction HADS A. WHR is not significantly related to anxiety (r_s=-.118, p=.26) and neither is current HbA1c (r_s=-.049, p=.64).

Retinopathy and Microvascular Disease

A negative relationship was also found between microvascular complications (retinopathy) and anxiety scores. Higher severity of retinopathy was correlated with lower HADS A scores (r_s=-.288, p=.002), higher general positive well-being (r_s=.214, p=.019), lower general stress (r_s=-.241, p=.010) and higher general well-being (r_s=.250, p=.007). Using partial Spearman's correlation, when controlling for age, this relationship remained significant for HADS A (pr_s=-.227, p<.05). However, it was not significant for general positive well-being (pr_s=.143, p=.085), general stress (pr_s=-.151, p=.074), or general well-being (pr_s=-.159, p=.064). Similarly, greater overall microvascular disease was related to lower HADS anxiety (r_s=-.260, p=.006), lower general negative well-being (r_s=-.205, p=.024), and lower general stress (r_s=-.173, p=.048). Using partial Spearman's correlation, when controlling for age, this relationship was attenuated; however, it remained significant with HADS A (pr_s=-.187, p<.05,) and not with general negative well-being (pr_s=-.115, p=.28), or general stress (pr_s=-.059, p=.58).

Using chi square, Low Severity Retinopathy - LSR (none/mild/observable retinopathy) and High Severity Retinopathy

HSR (referable/proliferative retinopathy) groups were compared across ratings for HADS A. Given that most participants' ratings were in the normal range, HADS ratings were recoded to groupings of low normal HADS score (0-3) high normal HADS score (4-7) and above normal HADS score (≥8). The counts, expected frequencies and percentages are presented in Table 7.6. Results of chi square statistic indicated that there is a significant association between normative rating of HADS anxiety and level of retinopathy, $\chi^2(2)=6.50$, $p<.05$. This seems to represent the fact that, for those in the LSR group, there was a lower than expected number with low normal HADS A scores and a higher than expected number with high normal and above normal HADS A scores. In contrast, for those in the HSR group there was a higher than expected number with low normal HADS A scores and a lower than expected with high normal and above normal HADS A scores. For those with maximal retinopathy, the majority of the group (56%) had low normal HADS anxiety score, whereas 30% with minimal retinopathy had a low normal anxiety score. A higher percentage of those with minimal retinopathy had high normal anxiety scores (37.5%) than those with maximal retinopathy (27.8%). A higher percentage of the group with minimal retinopathy had above average HADS A scores (32.5%) than the group with maximal retinopathy (16.7%).

Table 7.6 *Chi Square Cell Counts for HADS A by Retinopathy and by Age*

		HADS A Category			
		Low Normal (Score = 0-3) n (%)	High Normal (Score = 4-7) n (%)	Above Normal (Score = 8+) n (%)	Total n (%)
Min Ret	Count	12	15	13	40
	Exp	17.9	12.8	9.4	40
	% Min Ret	30.0	37.5	32.5	100
Max Ret	Count	30	15	9	54
	Exp	24	17.2	12.6	54
	% Max Ret	55.6	27.8	16.7	100

Min Ret=Minimal Retinopathy (None/Mild/Observable); Max Ret = Maximal Retinopathy (Referable/Proliferative); U60=Under Age 60; 60+=Over Age 60; Exp=Expected Frequency; HADS=Hospital Anxiety and Depression Scale

Age, retinopathy and hypertension (high blood pressure or taking blood pressure medication) were entered into multiple regression to determine significant predictors of HADS A score, as all three have been show to have a significant relation to HADS A in correlation. Although these factors are all positively correlated to each other, (i.e., age and hypertension, r_s=.244; age and retinopathy, r_s=.276; retinopathy and hypertension, r_s=.289, p<.01) there were no issues of multicollinearity identified to limit regression analysis (i.e. VIF=1.1; Tolerance<1; each variable loads highly on a separate dimension). In the final step of the analysis, age and hypertension

remained as significant predictors of HADS A score, $F(2,91)=8.219$, $p<.01$. The beta values for each step of the regression analysis are presented in Table 7.7.

Table 7.7 *Multiple Regression Results: Demographic and Health Predictors of HADS-Anxiety Score*

	B	*SE B*	ß	*t*	*p*
Step 1					
Constant	13.808	2.833		4.878	.000**
Age	-.101	.050	-.207	-2.033	.045*
Retinopathy Level	-.815	.888	-.095	-.918	.361
Hypertension	-2.886	1.184	-.248	-2.439	.017*
Step 2					
Constant	14.155	2.805		5.045	.000**
Age	-.111	.048	-.229	-2.307	.023*
Hypertension	-.313	1.153	-.269	-2.712	.008**

Analysis uses multiple regression with backwards stepwise entry
Retinopathy Level (Minimal/Maximal); Hypertension (Yes/No)
R^2=.161 for Step 1; Δ R^2=-.008 for Step 2 (ps=.36);, *p<.05 **p<.01

7.5.4. Question 4

Do immediate measures of well being relate to cognitive function?

General Intelligence

There was a positive relationship between IQ scores and some of the indicators of well being. Those with higher IQ had higher ratings on the WBQ for general energy (r_s =.175, p=.045), general positive well being (r_s =.222, p=.016), and general well-being (r_s =.190,

p=.03). These relationships were no longer significant when controlling for participant age through a Spearman's rho partial correlation for general energy (pr_s =.116, p=.13, one-tailed), general positive well being (pr_s =.165, p=.06, one-tailed), or general well being (pr_s =.111, p=.15, one-tailed). Those with higher IQ had lower scores on one indicator of negative well being, the HADS D rating (r_s =-.219, p<.05, one-tailed). This relationship remained when controlling for participant age (pr_s =-.194, p<.05, one-tailed).

Cognitive Domains

The results of Spearman's rho correlation, one-tailed (Appendix P) indicated that well-being scores were related to a restricted number of cognitive domains and age-adjusted cognitive change. The measure of executive function, Trail Making Test B (z score based on age norms) was negatively correlated with diabetes negative well being (r_s=-.220, p=.02). This relationship remained when controlling for age (pr_s=-.279, p<.01).

When investigating the diabetes factors that are predictive of the TMT-B score, it was found that microvascular disease was the only significant predictor of TMT-B scores. Microvascular total, age, and diabetes negative well-being score were entered into multiple regression. Both microvascular disease and diabetes negative well-being remained significant predictors of TMT-B score, F(2,90)=5.772, p<.01, explaining 11.4% of the variance in the TMT-B score, r^2=.114 for final model.

Table 7.8 *Well-Being, Demographic and Diabetes Health Predictors of TMT-B Score*

	B	*SE B*	ß	*t*	*p*
Step 1					
Constant	1.883	.331		5.688	.000**
Age	-.009	.006	-.167	-1.551	.124
Micro Total	-.209	.107	-.205	-1.960	.053
WBQ DNWB	.048	.019	-.253	-2.466	.016*
Step 2					
Constant	1.391	.096		14.434	.000**
Micro Total	-.264	.101	-.258	-2.603	.011*
WBQ DNWB	-.040	.019	-.209	-2.103	.038*

Analysis uses multiple regression with backward stepwise
Micro Total = Microvascular Total (combined retinopathy, neuropathy, nephropathy); WBQ DNWB = Well-Being Questionnaire Diabetes Negative Well-Being
R^2=.137 for Step 1 Δ R^2=-.023 for Step 2 (ps=.12), *p<.05 **p<.01

The test of short-term/working memory, Digit Span (z score based on age norms) had a positive relationship with well-being sores including general positive well being (r_s=.256, p=.006), general energy (r_s=.215, p=.02), and general well being (r_s=.196, p=.03) and had a negative relationship with HADS D (r_s=-.274, p=.008). Results of partial correlation using Spearman's rho indicate that these relationships remain when controlling for age for general positive well being (pr_s=.240, p<.05), general energy (pr_s=.197, p<.05), general well-being (pr_s=.173, p<.05), and HADS D (pr_s=-.237, p<.05).

Multiple regression was used to identify significant predictors of the Digit Span score (Table 7.9). Age, NART IQ and HADS D were entered into the analysis. In the final step of the model, NART IQ remained as the only significant predictor of Digit Span scores,

F(2,91)=13.51, $p<.01$, explaining 23% of the variance in the score, $r^2=.229$ for final model. There was a trend towards significance for the GPWB score (ß=.181, $p=.057$)

Table 7.9 *Multiple Regression: Well-Being, Age and IQ As Predictors of Digit Span Scores*

	B	*SE B*	ß	*t*	*p*
Step 1					
Constant	-1.225	.570		-2.150	.034*
Age	-.002	.004	-.046	-.466	.642
NART IQ	.022	.005	.420	4.389	.000**
WBQ GPWB	.028	.014	-.192	1.979	.051
Step 2					
Constant	-1.274	.558		-2.285	.025*
NART IQ	.022	.005	.411	4.396	.000**
WBQ GPWB	.027	.014	.181	1.931	.057

Analysis uses multiple regression with backward stepwise entry

WBQ GPWB = Well-Being Questionnaire General Positive Well-Being

$R^2=.231$ for Step 1 $\Delta R^2=-.002$ for Step 2 (ps=.64), *p<.05 **p<.01

Results of Spearman's rho correlation indicated that the age-adjusted estimate of cognitive change (A-ELCC) was related to a number of aspects of well being (Table 7.10). When controlling for age, the relationship of the A-ELCC score with HADS A, general energy, general well being, and diabetes negative well being becomes non-significant. The only significant relationships that remain are negative relationships between A-ELCC and general negative well being and general stress.

Table 7.10 *Correlation Between Ratings of Well-Being and Age-Adjusted Lifetime Cognitive Change*

Variable	A-ELCC	A-ELCC & Age
HADS-Anxiety	-.189 (.04)**	-.128 (.22)
HADS-Depression	-.145 (.08)	-.113 (.28)
WBQ General Negative Well-Being	-.255 (.007)**	-.209 (.04)*
WBQ General Energy	.175 (.046)*	.118 (.26)
WBQ General Positive Well-Being	.104 (.16)	.060 (.57)
WBQ General Stress	-.243 (.009)**	-.216 (.04)*
WBQ Diabetes Negative Well-Being	-.221 (.016)*	-.203 (.050)
WBQ Diabetes Stress	-.112 (.14)	-.114 (.28)
WBQ Diabetes Positive Well-Being	. 109 (.15)	.071 (.50)
WBQ General Well-Being	.235 (.01)*	.186 (.07)
WBQ Diabetes Well-Being	.214 (.02)**	.152 (.15)

Spearman's rho used for ALCC; Spearman's rho partial correlation used for ALCC & age,
one-tailed correlation values, *p<.05, **p<.01

Multiple regression was used to identify significant predictors of the A-ELCC score (Table 7.11). Age, NART IQ, retinopathy severity and General Negative Well-Being (GNWB) were entered into the analysis. In the final step of the model, retinopathy severity and GNWB remained as the only significant predictors of A-ELCC scores, $F(2,91)=6.756$, $p<.01$, explaining 13% of the variance in the score, $r^2=.129$ for final model.

Table 7.11 *Multiple Regression: Retinopathy, Well-Being, Age and IQ As Predictors of Age-Adjusted Estimate of Lifetime Cognitive Change*

	B	*SE B*	ß	*t*	*p*
Step 1					
Constant	-.461	1.673		-.275	.784*
Age	-.002	.012	-.016	-.143	.887
NART IQ	.009	.014	.067	.650	.517
Ret Level	-.537	.199	-.280	-2.694	.008**
WBQ GNWB	-.106	.047	-.240	-2.281	.025*
Step 2					
Constant	-.511	1.627		-314	.754
NART IQ	.009	.014	.064	.638	.525
Ret Level	-.545	.190	-.284	-2.863	.005**
WBQ GNWB	-.104	.044	-.236	-2.350	.021*
Step 3					
Constant	.521	.167		3.120	.002
Ret Level	-.556	.189	-.289	-2.940	.004**
WBQ GNWB	-.109	.044	-.247	-2.507	.014*

Analysis uses multiple regression with backward stepwise entry
Ret Level=Retinopathy Level x2 (Minimal-None/Mild/Observable and Maximal – Referable & Proliferative
WBQ GNWB = Well-Being Questionnaire General Negative Well-Being
R^2=.133 for Step 1 Δ R^2=.000 for Step 2 (ps=.89), Δ R^2=-.004 for Step 3 (ps=.53), *p<.05 **p<.01

7.6. Discussion

7.6.1. Question 1

What percentage of the study group is classified within each category on the HADS anxiety and depression scale?

Results indicated that this middle-aged to older group with T1DM showed many indications of positive psychological well being. Although in the current study, most of the participants indicated ratings of anxiety and depression within the normal range, there is a higher percentage within the normal range in the study group than found in the normative population (Crawford et al., 2001). Although there is research relating higher levels of depression to those with T1DM, there was a similar percentage that were classified in the normal range for depression in the UK study sample as in the study sample.

Only a small percentage of participants showed high levels (moderate or severe) of anxiety or depression that would indicate a probable clinical disorder, despite the fact that these study participants have a chronic disease that involves significant day-to-day management, dietary, and lifestyle limitations. The incidence of moderate and severe levels of anxiety and depression is lower than a previous clinic study (Lloyd et al., 2000) that found more than a quarter of the adults with diabetes (Type 1 & 2) rated anxiety and/or depression at the moderate and severe level. However, the clinic study did include a wide age range (18-80) and the current study is focused on middle age to older adults. Since well being is found to increase with age into the late 60s (Carstensen et al., 2011) one reason for the slightly lower rates of clinically significant depression and anxiety may be the focus on this older age group. The current study sample was self-selected and included those with T1DM only. The previous

study may have included some with diagnosed psychological disorders, however the current study did not. In a study comparing older adults (mean age = 61.6) with T1DM and controls (Brands et al., 2006), the researchers also concluded that the group with diabetes did not show a difference in level of psychological distress and a lower rate of depression than reported in other studies.

7.6.2. Question 2

Do measures of well being relate to demographic variables?

In the study sample, participant age had the strongest relationship to participant's ratings on the well-being scales. With few exceptions, older age was related to higher ratings of positive well being and lower ratings of negative well-being. This reflects a well-established finding highlighted in the longitudinal study of a non-clinic sample, with steady gains in emotional well being from age 20 into the late 60s only leveling in the 70s and a linear gain in emotional stability into the 9th decade (Carstensen et al., 2011). One theory is that this difference could be due to changes in emotion regulation between older and younger adults (Urry & Gross, 2010). As well, another study of T1DM reported that older age is a protective factor associated with lower HADS anxiety and depression scores (Collins et al., 2009). This highlights the fact that despite dealing with a chronic disease, this group shows similar positive relationship between age and well being that is a hallmark of normal ageing. This highlights the need to separate groups by age when estimating the rates of anxiety and depression in this population.

In the study sample, women had higher ratings of general negative well-being and diabetes specific ratings of negative well-being. These scales both include items relating to worry and sadness. Women also rated themselves above the average on the HADS A compared to men. However there was no significant relationship with HADS D and there were not as clear findings regarding ratings of anxiety as there has been in previous studies. This is not consistent with study on the UK normative sample for the HADS (Crawford et al., 2001). In the population study, women rated themselves higher on both the anxiety and depression scales, even when controlling for age. As well in a study of anxiety and depression symptoms in diabetes, female gender was associated with higher anxiety scores, however was not a significant predictor of anxiety scores (Collins, et al., 2009). Older age may diminish the sex differences on anxiety and depression ratings identified in younger age groups.

7.6.3. Question 3

Do measures of well-being relate to diabetes health variables*?*

Duration was related to a better sense of diabetes-specific well-being. This includes feeling adjusted to diabetes, feeling satisfied and positive with diabetes management and feeling can cope with diabetes challenges. It is not known whether this evaluation of diabetes well-being is particular to middle-aged and older adults or is a function of becoming more accepting of diabetes over time. Consultants and patients can capitalize on this positive outlook in self-management goals.

In the current study, measures of mean, recent and current glycaemic control were specifically related to measures of diabetes well-being. Those with higher HbA1c showing lower diabetes well-being and greater diabetes stress. These scales includes specific items about satisfaction and feelings of diabetes management suggesting a correspondence between participants' feelings about the management and their actual HbA1c value. An association with depression scores was identified for one measure of HbA1c, the long-term mean, and not for more recent or current values. Van Tilburg and colleagues (2001) found that that Beck Depression Inventory scores, below the cut-off for clinical depression, were positively related to current HbA1c values for a small group with T1DM. They suggested less self-monitoring of blood glucose may mediate this relationship. The fact that current HbA1c and depression scores are not correlated for this older group of adults with long-duration of diabetes suggests that evaluation of depressed mood is likely not linked to evaluation of current management of HbA1c and having more depressive symptoms is likely not enough to influence current HbA1c. The finding in one previous study showed that therapeutic treatment of depression does not result in better HbA1c values over the course of a year (Georgiades et al., 2007), suggesting that depression isn't directly influenced by a persons' current level of control over diabetes. Participants' ratings on the WBQ Diabetes Negative Well-Being Scale also indicate that most of the study participants did not feel depressed about diabetes. This also suggests that immediate evaluation of

depressive symptoms is not directly influenced by current values of glycaemic control. It may be that depression is a result of chronic hyperglycaemia as suggested by Van Tilburg and colleagues (2001). This is a topic for a future prospective study.

In multiple regression mean HbA1c was retained as the sole significant positive predictor of HADS D scores. Even though retinopathy is positively correlated with HbA1c, there was a trend for retinopathy to have a negative association with HADS D scores in the final model. Results of meta-analysis indicate that depression is associated with a higher level of complications in T1DM (De Groot, Anderson, Freedland, Clouse, & Lustman, 2001), however the authors did note that three studies showed trends towards inverse relationships, with lower depression associated with higher complications.

Both retinopathy and a combined measure of microvascular disease were negatively related to HADS A, even when controlling for age. When the group was split by retinopathy level those with high severity retinopathy had low normal HADS A scores and more than expected had high normal and above normal (mild/moderate) HADS A scores. The opposite pattern was found for those with low severity of retinopathy. It is possible that for those with T1DM, having some concern about health may promote better health. “Optimism and positive thinking can derail us is if they lead us to ignore or discount important cues and warnings.” (Norem & Chang, 2002, p.998). In their study on the psychological aspects of adolescents with diabetes, Dusan

and colleagues (2010) found that teenagers with good metabolic control (<7.5%) had more problems with anxiety, relied on others more in dealing with stress, and used optimism and positive attitude as a coping style. The authors suggest it confirms the hypothesis that anxiety has a protective influence through fear of chronic complications and can be "conditionally called 'functional' anxiety" (Dusan et al., 2010, p.1792). Results suggest that some level of worry may expected and beneficial to a patient with chronic disease who has high need for self-responsibility for monitoring and management and significant consequences for sub-optimal management. This is also supported by the finding that a higher than expected number of participants with high severity of retinopathy had low normal HADS A scores. The idea of functional anxiety may apply here with those with low worry related to higher severity of complications, however this would need to be investigated in a prospective study.

To look at the importance of age in the prediction of anxiety scores, age was included in regression analysis along with retinopathy and hypertension. It was found to have a significant negative relationship with retinopathy level. Results highlighted that both age and hypertension were significant negative predictors of HADS A scores. Both older age and having hypertension were related to lower anxiety scores. These results highlight the importance of the positive relationship between age on well being even in this group with a chronic health condition and is also suggestive of the possibility of a functional role of anxiety symptoms of worry.

These results highlight the importance of using clinical interview in the study of anxiety disorders and diabetes to differentiate those with anxiety disorder and those with functional worry stemming from the management of a chronic disease with significant consequences to future quality of life. In a systematic review of screeners for depression, researchers concluded that the HADS and other similar self-rating scales identified a high rate of false positives and emphasized that these types of tools are not diagnostic in and of themselves and not intended for the purpose of assessing symptom severity (Roy, Lloyd, Pouwer, Holt, & Sartorius, 2011). It may be that a "normal range" of anxiety for those with T1DM (as measured by self-report), encompasses a higher range of scores on the HADS than for people without a chronic disease requiring high self – management. Since the HADS is used as a quick screen for depression and anxiety in hospital settings, the negative evaluation of above normal scores may lead to over-identification of problems and advice and treatments that may not lead to the best diabetes health outcomes for patients. Further identification and clarification of this functional level of worry for groups with T1DM may help to better tailor advice that would ultimately promote better disease self-management.

7.6.4. Question 4

Do immediate measures of well being relate to cognitive function?

In the current study, well-being scores were related to two of the individual cognitive domains including executive function and short-term/working memory as well as the overall estimate of lifetime

cognitive change (A-ELCC). Both total microvascular disease and a measure of diabetes-specific negative well being on the WBQ are significant negative predictors of executive function score. For short-term/working memory scores, only NART IQ remained as a significant positive predictor with a trend towards an additional positive significance for a measure of general positive well being. Both retinopathy level and a measure of general negative well being was predictive of lower estimate of lifetime cognitive change (indicating greater cognitive decline). These results highlight the importance of psychological variables in understanding cognitive function.

There is one study of cognition in older adults with T1DM that also includes measures of psychological well being (Brands et al., 2006). These researchers did not find a relationship between the well-being measures they used and measures of cognitive function, however different measures of well being were used. The measures highlighted are those tailored specifically for people with diabetes (WBQ), also speaking to the importance of designing population-specific measures to evaluate well being in this group

7.6.5. Conclusions

What do the results tell us about cognitive ageing in T1DM and its relationship with theories of cognitive ageing?

These results speak to the positive outlook of older adults that can be harnessed when setting treatment goals within this group. These encouraging results may be related to the older age of this T1DM group given the finding in ageing studies that well being increases

through the late 60s (Carstensen et al., 2011). Psychological well-being is a component of successful ageing (Young, Frick, & Phelan, 2009), and these results highlight an aspect of successful ageing in this group despite daily living and management of a chronic disease. The possibility that there may be a functional level of anxiety that is related to less severe microvascular complications and an overall positive outlook in this group, requires careful balance to promote worry that is helpful and not debilitating.

The relationship between feelings of negative well being and cognitive function in this group was specifically identified in areas identified in ageing research (working memory and executive function) and related to cognitive decline. This speaks to the importance of monitoring and addressing well being to promote the best cognitive outcomes in ageing for this group.

STAC theory (Park & Reuter-Lorenz, 2009) suggests that new learning, cognitive engagement, and exercise promote scaffolding or the brain's ability to make functional changes that maintain cognitive function. Cognitive reserve theory identifies leisure activities, social experiences, and exercise among factors that increase cognitive reserve (Tucker & Stern, 2011). Given the positive attitudes and well-being identified in this group, this general sense of well-being may potentially facilitate engagement in these activities in this middle-aged to older adult group. Results from both the cognitive study and the investigation of MCI support the positive role of exercise and cognitive activity on cognitive function in this group. The fact that

well-being is also related to key areas of cognitive function identified in ageing research, suggests a role for a focus on well-being in minimizing cognitive changes.

Chapter 8
Evidence of Functional Brain Ageing in T1DM with Microvascular Disease

8.1. Introduction

In comparing younger and older groups with T1DM, although older groups show areas of greater deficit, these cognitive deficits are not thought to be beyond the trajectory expected in the normal ageing process (Ryan, 2005). As well, when comparing older individuals with T1DM to age-matched controls, Brands and colleagues (2006) concluded that T1DM does not have a significant impact on the brain structure or cognitive function. Functional neuroimaging has the potential to identify brain functioning that suggests an early ageing process even when there appears to be little observable change in cognitive function.

In the normal brain ageing process, changes in brain function have been viewed as a scaffolding process to compensate for structural brain changes (Park & Reuter-Lorenz, 2009). Preservation of cognitive function may be seen despite the presence of functional brain differences between young and old groups through functional compensation or preservation of cognitive performance through recruitment of non-task related brain areas (Rajah & D'Esposito, 2005). For example, a move from neural specificity in younger adulthood to differentiation in ageing can support maintenance of cognitive processes (Cabeza, 2002). Baltes & Lindenberger (1997) suggest this process of de-differentiation is highlighted by the link

between sensory and intellectual function in ageing suggesting these processes are distinct in younger adults and become entwined in ageing. There are several researchers that highlight common changes found in normal brain ageing detailed below.

8.1.1. Default Mode Network in Ageing

The default mode network (DMN) includes the medial prefrontal and lateral parietal regions of the brain that are connected and more active during rest, and suppressed during tasks. The intrinsic activity in these regions is correlated, jointly elevated at rest, and diminished during active cognition. Damoiseaux and colleagues (2008) identified posterior and anterior resting state networks that showed lower activity in older compared to younger adults. The posterior part of the DMN includes the posterior cingulate and bilateral superior parietal regions. The anterior part of the DMN includes the superior and middle frontal gyri, posterior cingulate, bilateral middle temporal gyrus, and bilateral superior parietal regions. Their research showed that decreased activity in the anterior DMN was associated with cognitive decline. Buckner, Andrews-Hanna, and Schacter (2008) indicate that the core regions identified as part of the DMN based on Brodmann's Area classification include the ventral medial prefrontal cortex (vmPFC; BA 24, 10, 32), posterior cingulate/retrosplenial cortex (BA 29/30, 23/31), inferior parietal lobule (BA 39/40), lateral temporal cortex (BA 21), dorsomedial prefrontal cortex (dmPFC; BA 24/32/10/9) and the hippocampal formation (hippocampus, parahippocampal cortex, entorhinal cortex). In a study of task-

associated deactivation of the DMN in older adults, Persson, Lustig, Nelson, & Reuter-Lorenz (2007) found that older adults did not decrease resting state activation as much as younger adults in medial frontal, anterior cingulate and posterior cingulate when engaged in a task.

8.1.2. Posterior-Anterior Shift in Ageing (PASA)

Ageing researchers have found that there is a reduction of activity in occipital and temporal areas that go along with increases in frontal activity in normal ageing (Davis et al., 2008). This activity is independent of task difficulty and is compensatory (i.e. prefrontal cortex activity is correlated positively with cognitive task performance and negatively correlated with occipital activations). These researchers suggest that decreases in occipital areas reflect deficits in sensory processing. They suggest the same pattern happens in task-related deactivation of the DMN. Older adults deactivate anterior regions of the DMN to a greater extent than posterior regions of the DMN.

8.1.3. Neuroimaging in Ageing Summary

A recent review by Reuter-Lorenz and Park (2010) summarized the findings of neuroimaging studies of younger groups 18-30 and older groups aged 65 and older. Differences between the younger and older groups included less task-induced deactivation of the DMN (i.e., maintenance of DMN activation) with increased task difficulty, prefrontal overactivation (i.e., stronger and/or more sites of frontal

activation) and less connectivity and less overall activity in resting state. Waiter and colleagues (2008) found that older adults who showed cognitive decline ("decliners") showed an absence of activation that was significantly negatively or positively correlated with task difficulty. Those who maintained cognitive function over time ("sustainers") showed a similar pattern of negative posterior correlations and positive frontal correlations with an increase in task difficulty as the pattern shown in the whole group and in comparison to younger adults.

8.1.4. Accelerated Brain Ageing

Given that evidence of brain ageing is not directly reflected in observable cognitive change, the question remains unclear whether the effects of long-term hyperglycaemia, specifically retinopathy, could indicate an increase in microvascular burden in the brain that relates to signs of accelerated ageing in individuals with T1DM. Do individuals with retinopathy show premature brain ageing of vulnerable areas? If there are signs of accelerated ageing, functional performance in these middle age participants (45 to 65) with T1DM should look similar to the research on functional activation and deactivation in older adult groups.

Specifically:

- Prefrontal overactivation - stronger, more sites: inferior frontal gyrus, dorsolateral PFC (Davis et al., 2008)

- Less task induced deactivation of default network - default activation during task: medial PFC, posterior cingulate, precuneus, inferior parietal (Persson et al., 2007)
- Less connectivity in default network - less activity in resting state (Damoiseaux et al., 2008)
- Pattern comparable to "decliners" on the Waiter and colleagues (2008) inspection time task

8.2. Study Aims

Results of the cognitive study suggest that it may only be with the presence of blood-sugar related changes in small blood vessel integrity, as in retinopathy and other microvascular diseases, that patients with T1DM experience mild changes in cognitive function. This finding was further tested through functional neuroimaging to determine whether there is evidence of accelerated cognitive ageing in this group. In this study, a subgroup of participants from the cognitive study with and without microvascular disease (retinopathy) with varying levels of blood glucose control was selected for follow-up using functional magnetic resonance imaging (fMRI).

8.3. Study Questions

1. Does neural activation (as indicated by the blood oxygen level dependent (BOLD) response in fMRI), when completing a cognitive task and at rest, differ between groups with high severity retinopathy and those with low severity retinopathy?

2. Does BOLD activation in the high severity retinopathy group resemble patterns found in normal ageing?

8.4. Ethics

A favourable ethical opinion was obtained (Appendix Q) through the Tayside Committee on Medical Research Ethics A, an arm of the East of Scotland Research Ethics Service for the National Health Service (NHS). Approval to conduct the study on NHS Sites and with the assistance of NHS staff was sought through the NHS Research and Development Office (Appendix Q). Ethical approval was also sought and obtained through the University Teaching and Research Ethics Committee (UTREC) for the University of St. Andrews.

8.5. Methods

8.5.1. Participants

A subgroup of 30 participants from the Cognitive Study who were evenly sampled from those who have high severity retinopathy (referable and proliferative retinopathy) and low severity retinopathy (none/mild/observable retinopathy) between the ages of 45 and 65 were recruited to take part in the neuroimaging study. Potential participants were contacted by phone. Participants who were interested in the study and who met the inclusionary/exclusionary criteria received an information sheet detailing their participation. If the participant agreed, a time for MRI scan was arranged. Informed consent was completed before the MRI scanning session.

Inclusion Criteria

The same inclusionary criteria used for the cognitive study (Study 1) applied to the neuroimaging study (Study 2), however only participants between 45 and 65 years old were invited to take part.

Exclusion Criteria

The same exclusionary criteria used for the cognitive study (Study 1) applied to the neuroimaging study (Study 2). Participants were excluded if they had conditions or characteristics that would preclude MRI scanning including:

- metal implants, foreign metal objects in body
- medical devices (e.g. pacemaker, surgical clips)
- pregnancy
- internally implanted insulin pump or external (tube/tubeless) insulin pump that cannot be safely removed for a period of 60 minutes.
- currently taking part in other clinical or research MRI scanning
- recent surgery (past 6 weeks)

Emotional or physical limitation to entering the MRI scanner

- Fear of confined spaces (i.e., Claustrophobic)
- Physical limitation that impedes ability or comfort to stay still lying down for extended time in the scanner (e.g. tremors)

8.5.2. Procedure

The sequence of events in the MRI procedure is graphed in a flow chart in Appendix S. MRI scanning took place at the Clinical Research Centre (CRC) at Ninewells Hospital, Dundee.

Blood Glucose Testing

After signing consent, participants checked their blood glucose. If blood glucose was below 5mmol/l the participant had a glucose drink and biscuit and then re-checked blood glucose to ensure it was over 5 mmol/l. This was a higher threshold than used in the cognitive study to ensure that the risk of participants having a hypoglycaemic event in the scanner was low as they would be in the scanner for approximately 60 minutes.

Training on Cognitive Tasks

The researcher reviewed the sequence of events in the scanner with the participant and provided baseline training on the cognitive tasks that they will encounter during the fMRI experiments. The participant then completed training on the two tasks they would complete in the MRI scanner (Appendix T), until the examiner and participant were confident that they understood the tasks.

Preparation for MRI

After completing the NHS Tayside MRI Patient Safety Questionnaire, and changing into scrubs, the radiographer and physicist prepared the participant for the scanning session. The MRI physicist prepared the necessary equipment (headphones, goggles, response buttons) and ensured all the equipment was functioning correctly. Corrective goggles were used for the participant to be able to view the computer screen, and was adjusted specifically to suit each participant's vision.

Emergency Protocols

Participants were provided with an emergency squeeze bulb in case they experienced any distress during scanning. They were able to use this to alert the imaging staff that assistance was required or they would like to stop the scanning. None of the participants had to use this emergency alert and all completed the MRI scanning. Once the participant entered the MRI and had first-hand experience of this environment, they were asked again if they were still willing to proceed. If so, the MRI protocol was initiated. Participants could stop participation at any time, however all completed the tasks.

MRI scanning

The radiographer provided instructions before each section of scanning to indicate the purpose of the sequence, and to tell the participant what they would be required to do during the session (e.g., lay still with eyes closed, or asked to read instructions for the specific cognitive task). All of the fMRI imaging was completed in one session. The total scanning session was 60 minutes on average. The presentation of tasks was chosen to be similar to previous research protocols and to minimize scanner time for participants.

8.5.3. fMRI Data Acquisition

Functional MRI tasks were chosen because they were key features of cognitive ageing, and were highlighted in this cognitive study and other studies of T1DM and cognition. The tasks chosen had been well tested in other fMRI studies of diabetes and/or ageing

(Wessels et al., 2006; Waiter et al., 2008, 2009, Damoiseaux et al., 2008). This included a measure of working memory (n-Back), a measure of processing speed (inspection time), and resting state. The total time of each task was between 5 to 8 minutes to take into consideration the older age and physical limitations of some of the participants that would make it physically difficult to stay focussed and still for tasks for an extended time. The instructions and visual stimuli were presented on a computer monitor and viewed through goggles attached to the head coil. The MRI physicist applied the necessary vision correction through the goggles prior to scanning. Participants were provided two pushbutton boxes, one for each hand to allow the software to log the timing and responses to the task.

Working Memory: N-back

During the n-back task, participants are shown English letters and asked to respond by pressing the right button to a specific target letter and the left button to all other letters. In the easy version of the task, for each letter shown and the participant was asked to press the right button when a target letter X appeared (0-back) and the left button to any other letter. On the hard version of the task, to increase working memory load, the participant was asked to press the right button if the letter was the same as the one presented two trials back (2-back) and the left button to all other letters. An example of the appropriate responses to a mock sequence of letters on the 2-back task is provided showing the trial; letter and corresponding correct button push in Table 8.1

Table 8.1 *2-Back Example*

Trial	Letter Displayed	Correct Button Response
1	A	L
2	B	L
3	C	L
4	B	R
5	B	L

Dr. Stephen Nicholas, an MRI Physicist at the Clinical Research Centre (CRC) at Ninewells Hospital, Dundee programmed the n-back task using Presentation software (Neurobehavioral Systems Inc., CA). To minimize scanner time and frustrations for participants on this task, only the 0-Back and 2-Back conditions were used. In the previous fMRI studies mentioned, these were the only contrasts on which a group with T1DM with and without retinopathy differed (Wessels et al., 2006) and the only contrast that differentiated groups in a study of cognitive ageing (Waiter et al., 2009). The task was presented in a block design interleaving 4 epochs each of 0-back and 2-back with 14 trials in each block and an inter-stimulus interval (ISI) of 2.5 seconds (1 s letter, 1.5 s blank). Each block lasted 32.5 seconds including 5 seconds for instructions at the beginning of each block. Each participant completed one run (4 epochs) of the n-back task. There was no fixation stimulus used. Behavioural measures included response accuracy and reaction time.

The run was presented in the same order (0-back first, 2-back second for each epoch) such that all participants started with the easy version of the task to ensure initial success and motivation. In both the 0-back and 2-back blocks the probability of the item being a target was 29% (4/14). The occurrence of the target letter was different for each block to reduce the chances of learning a response set. In the 2-back block, there was a 29% chance the letter would be a repeated letter (i.e. a distractor letter seen before in the block either 1 back or 3 back) and a 43% chance (6/14) the letter would be new within the block.

Resting State: Default Mode Network

Resting state data was collected as in previous fMRI studies of ageing (Damoiseaux et al., 2008) in investigation of the default mode network. Participants were asked to lie still in the scanner with their eyes closed while scanning proceeded with similar imaging parameters as in the n-back task.

Processing Speed – Inspection Time

Inspection time is a simple visual discrimination task. Two parallel vertical lines of obviously different lengths are shown on a computer screen to the participant for less than a second. Participants were asked to indicate the side on which they saw the longer line shown in *Figure 8.1*. Trials were varied in difficulty by showing the line pairs for varying lengths of time, which affects the likelihood of accurate performance. Harder trials were associated with shorter stimulus duration.

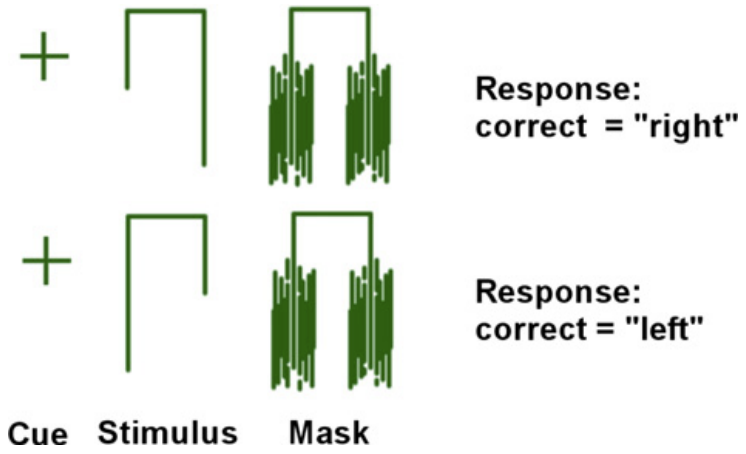

Figure 8.1 Inspection time stimulus showing correct responses. Image from Waiter and colleagues (2008), reprinted with permission of author.

The participant indicated the side on which they saw the longer line by pushing the left button with the left index finger if the longest line was on the left, and by pushing the right button with the right index finger if the longest line was on the right.

Participants were trained on the task before going into the scanner to provide familiarity with the task instructions and address any questions and provide practice to increase the chance of all participants responding correctly on this task. The threshold of inclusion for the data of a particular participant was above a threshold of 90% correct (31.5/35) for highest duration (97ms) and above chance (17.5/35) on the shortest exposure. Waiter and colleagues (2009) also used a threshold of 90% correct (18/20) on the inspection time task for the 100 ms exposure, therefore the same threshold was used in this study.

Dr. Gordon Waiter, MRI Physicist at the University of Aberdeen, provided the Presentation software syntax as the basis for programming the inspection time task (Presentation software, Neurobehavioral Systems Inc., CA). Waiter and his colleagues (2009) used this programming in their study, however they used a 1.5T Scanner and presented visual stimulus on a screen with a higher refresh rate than a typical computer screen. In the original studies (Waiter et al., 2008, 2009) 2 inspection time runs of 20 trials were presented at each of eight durations (6, 12, 25, 37, 50, 75, 100 and 150 ms). Only the time durations of 25, 37, 50 and 75 ms were included in analysis in the previous study (Waiter et al, 2008). The shortest time presentations were excluded because older adult groups did not show a difference in brain function at these levels of presentation and responding was below chance level. The longest duration showed 100% accuracy and also no differentiation between groups. For the purposes of the current study, the presentation of the task was shortened by eliminating the shortest duration presentations and some of the longest time presentations and optimized for the 3T scanner at the CRC by MRI Physicist, Dr. Stephen Nicholas. In the current study there were 5 stimulus durations used (15, 31, 48, 82, & 97 ms). More practically, at the shortest time (6ms) this presentation was not possible at the CRC due to a lower refresh rate of the computer screen available for stimulus presentation than available in the Waiter and colleagues study (2008).

The inspection time task is presented in an event-related design and optimized for the 3 T scanner. There was only one inspection time run in this study with 35 trials. The trials are presented in the same random order for each participant. The inter-stimulus interval (ISI) is 2 seconds. Behavioural measures included response accuracy and reaction time.

8.5.4. Brain Imaging Parameters

Scanning was performed on a Magnetom Trio 3.0 T scanner (Siemens Healthcare, Erlangen, Germany), using a standard 12-channel phased array head coil. The protocol for the structural and functional MRI is shown in Table 8.2.

After the structural scans, T2*-weighted gradient-echo (GRE) echo-planar images (EPI) were obtained in the axial orientation for the n-back task with a repetition time (TR) of 2.5s and echo time (TE) of 30 ms, slice thickness 3.0 mm, matrix 80, field of view (FOV) 240 x 240 mm (in-plane resolution 3.0 x 3.0 mm), and flip angle of 90º. Fat saturation and parallel imaging (acceleration factor of 2) were used to minimize chemical shift and distortion artifacts. There were 130 volumes for the n-back task made up of 37 slices/volume. The total scanning time for the n-back task was 5 minutes and 39 seconds. The same parameters were used for the inspection time task and for the resting state data. The differences were that for inspection time there was a shorter TR (2.2s) and there were 210 volumes collected for the inspection time task with 37 slices per volume. The total scanning time for the inspection time task was 7 minutes and 42 seconds. There were

140 volumes collected for resting state fMRI. The total scanning time was 5 minutes and 49 seconds. The Siemens System runs four "dummy" scans prior to the fMRI acquisition to ensure the fMRI signal has reached a steady state. These dummy scans do not form part of the data and the first synchronization pulse is only sent after these dummy scans have finished. Therefore, none of the acquisition volumes were discarded for data analysis.

Table 8.2 *Imaging Parameters and Timing for Structural and Functional MRI Sequences*

MRI Sequence	Purpose	Imaging Sequence	Imaging Orientation	Time in Minutes
Localiser	Template figures for placing slices in correct position	Low-resolution GRE	3 plane	0.13
Structural Scan 1: T1	High Resolution 3D images for morphometry.	T1 3D MP-RAGE (magnetisation Prepared-Rapid Acquisition Gradient Echo). 1 mm isotropic resolution.	Sagittal	4.26
Structural Scan 2: T2	Identification of lesions	T2 3D TSE (Turbo Spin Echo). 1 mm isotropic resolution	Sagittal	4.43
fMRI n-back run	data acquisition for working memory task	T2* GRE-EPI.	Axial	5.39
fMRI resting state run	Data acquisition for default mode network	T2* GRE-EPI	Axial.	5.59
fMRI inspection time run	Data acquisition for processing speed task	T2* GRE-EPI	Axial	7.42

8.5.5. Statistical Analysis

Behavioural Analysis

SPSS Version 19.0 (SPSS Inc., Chicago, IL, www.spss.com) was used to perform statistical analysis on the reaction time and accuracy data from the cognitive tasks.

Image Pre-processing

Initially, DICOM files were converted to Nifti format. SPM8 software (www.fil.ion.ucl.ac.uk/spm) was used to analyze the images. Pre-processing steps and parameters for n-Back, resting state and inspection time included:

1. Slice time correction: correction for acquisition delay between slices (37 slices, slice order=interleaved, middle reference slice = 37). Repetition Time (TR) =2.5 s for n-Back and resting state. TR=2.2 s for inspection time. Echo Time (TE) = 30 ms
2. Realignment: within subject registration motion correction realignment to first image of each series using rigid body affine transformation (translation <5mm for all subjects)
3. Normalization: warped to standard SPM 8 EPI template using 12-parameter affine transformation with a 2x2x2 mm voxel size
4. Smoothing: realigned and normalized images were smoothed with a 6mm full width half maximum Gaussian kernel

The first level within-subject analysis was completed following a General Linear Model approach. Information about the timing of

stimuli and responses were obtained from the Presentation log file for both the n-Back and the Inspection Time tasks.

N-back Random Effects Analysis

First-level statistical analysis for the n-back epoch data, followed the same process described by O'Connor, Han, & Dobbins (2010). Participants were treated as a random-effect and volumes as temporally-correlated time series. This was modeled by convolving a canonical hemodynamic response function (HRF) provided in SPM 8 along with delta functions that mark the onset of each condition from the presentation of the stimulus letter of the n-back test. Incorrect responses were grouped into a variable of no interest and not included in the analysis. Parameter estimates for the best-fit canonical HRF for the easy and hard conditions of the n-back task were used in pairwise contrasts and stored separately as an image for each participant. Images were tested against the null hypothesis of no difference between conditions using one-tailed, repeated measures, *t*-tests. Activations were considered significant if they had a voxel-extent of 5 or more and exceeded a threshold of $p<.001$.

Second-Level random-effects analyses were performed to compare groups with high severity retinopathy (HSR) and low severity retinopathy (LSR). A factorial ANOVA was used to investigate the interaction of age (young/old) and retinopathy (LSR/HSR) on BOLD activation. Estimated by beta values of BOLD signal activity generated through the second-level fMRI analysis and extracted using MarsBaR (Brett, Anton, Valabregue, & Poline, 2002) were used to examine the

direction of differences in regional brain activity between the LSR and HSR groups.

Resting State Analysis

Resting state analysis of functional connectivity was completed using the method described by O'Connor and colleagues (2010). Dr. Akira O'Conner at the University of St. Andrews provided the MATLAB program for this analysis. Functional connectivity analysis was examined on timecourses from one 4mm diameter region of interest (ROI). The ROI was created using MarsBaR software (Brett et al., 2002) to make a sphere around the central coordinate.

The research defined seed ROI in the ventromedial prefrontal cortex (vmPFC) was chosen as it had been identified as part of the Hippocampal-Cortical Memory System (HCMS; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). The Montreal Neurological Institute (MNI) coordinates of this region are x=0, y=51, z=-7; this is situated approximately in Brodmann area (BA) 10. This seed ROI is depicted on the brain image in Figure 8.2.

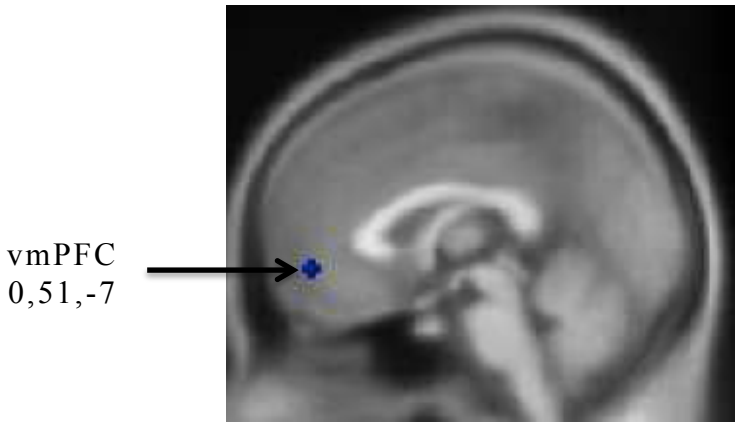

Figure 8.2 Location (including MNI coordinates) of the ventromedial prefrontal cortex (vmPFC) seed region used in resting state analysis.

Following the method outlined (O'Connoret al., 2010), the seed region was entered as a covariate of interest along with sources of non-specific variance (a total of 18 including 6 movement parameters, signal from spheres in the left lateral ventricle, deep cerebral white matter in left hemisphere and averaged across the whole brain, along with 9 first order derivatives of these covariates) using the same threshold as the functional data, $p<.001$, 5 voxel extent. This shows areas whose activation covaries with the seed regions scan-by-scan after nonspecific effects are controlled. Connectivity for the whole group, low severity retinopathy group (n=15) and high severity retinopathy group (n=15) were analyzed separately.

Inspection Time Random-Effects Analysis

Analysis of the event-related inspection task followed the method described in the study by Waiter and colleagues (2008).

Functional activity was modeled using one regressor for trials with correct responses and one for incorrect responses. The vector of stimulus onsets were convolved with a canonical hemodynamic response function provided in SPM 8, resulting in 10 predictors of brain activity for the inspection time run, 5 for correct responses and 5 for incorrect responses.

Second level random-effects analyses were performed to compare groups with high and low severity of retinopathy on easy and hard conditions of the Inspection Time tasks. Inspection Time analysis focused on BOLD activation associated with correct responses. Inspection time durations were weighted for increasing task difficulty for correctly answered trials using a linear weighting of inspection time durations in a manner comparable to Waiter and colleagues (2008). This weighting was recommended by Dr. Waiter as it would provide a near linear weighting based on duration (-1.00, -0.67, -0.25, 0.67, 1.25). Regions of positive and negative correlation with inspection time difficulty were determined by providing a linear weighting for the 5 inspection time stimulus durations using the regressors associated with correct responses only. A significance level of $p<.005$ uncorrected, with a 10 voxel extent was used for voxel-wise multiple comparisons at the group level in line with the recommendation for using less strict threshold values to balance Type I and Type II errors in functional neuroimaging studies of complex cognitive processes (Lieberman & Cunningham, 2009).

8.6. Results

8.6.1. Demographic Comparison of Retinopathy Groups

Thirty participants were recruited for the neuroimaging section of the study according to the highest reported rating based on the Scottish Diabetic Retinopathy Grading Scheme (SDRGS; 2007). Two groups were formed, with 15 participants each, the low severity retinopathy (LSR) group (none, mild or observable background diabetic retinopathy) and the high severity of retinopathy (HSR) group (referable background diabetic retinopathy/referable maculopathy, proliferative retinopathy or laser treated retinopathy). The comparison of demographics between the two groups is presented in Table 8.3. There was no difference between groups in age, education, gender, or premorbid IQ.

Table 8.3 *Comparison of Demographic Variables by Retinopathy Group*

	LSR (n=15)	**HSR (n=15)**	***t* (28)**	***U***	**$\chi^2(1)$**	***p***
Age $\bar{x}$ *(SD)*	52.62 (5.43)	53.61 (5.66)	-.488			.64
min-max yrs	45-62	45-64				
§Education (*Mdn*)	13.0	11.0		87.5		.30
min-max yrs	10-20	10-25				
Female (n)	9	8			.136	.99
†NART IQ	3.42_a(.601)	3.38_a(.980)	.145			.88
$\bar{x}$ *(SD)*	113.9_b(3.85)	113.7_b(6.03)				
min-max IQ	109-122	105-124				

2-tailed significance reported.

§Education could not be normalized, instead used non-parametric Mann Whitney U.

†NART IQ was transformed for analysis due to non-normal distribution (Reverse Square Root). Both transformed and non-transformed means are provided for ease of understanding.

a. Values for reverse square root, with *t* & *p* value

b. Original, untransformed values (not used in analysis – *t* &*p* value not reported)

The LSR and HSR groups were also compared on diabetes health variables reported in Table 8.4. It was expected that the HSR group would have greater diabetes health variables than the LSR group.

Table 8.4 *Comparison of Diabetes Variables by Retinopathy Group*

	LSR (n=15) $\bar{x}$ ***(SD)***	**HSR (n=15)** $\bar{x}$ ***(SD)***	***t* (28)**	***p***
Duration Diagnosis	26.7 (10.5)	28.2 (10.3)	-.382	.70
min-max years	11.5-43.1	13.8-49.0		
Age of Onset	25.91 (10.8)	25.44 (10.2)	.120	.90
min-max years	7.0-41.8	4.6-46.0		
Mean HbA1c	7.9 (.80)	8.7 (.60)	-3.07	.02*
min-max %	6.0-9.0	7.5-9.7		
†Micro. Disease	$.562_a$ (.28)	$.908_a$ (.24)	-3.65	.002**
	$.387_b$ (.27)	$.879_b$ (.51)		
min-max	0.0-1.07	0.4-2.13		
§Insulin Resistance	$.806_a$ (.13)	$.745_a$ (.15)	1.167	.26
(eGDR)	6.68_b (2.0)	5.89_b (2.2)		
min-max	3.8-10.5	2.8-10.6		

*$p<.05$, **$p<.01$; 2-tailed significance reported.

† Micro Disease=Microvascular Disease, was transformed for analysis (Square Root).

§ The variable insulin resistance was transformed for analysis (log 10), lower eGDR = greater insulin resistance

For all transformations, both transformed and non-transformed means are provided

a. Values for reverse square root, with *t* & *p* values

b. Original, untransformed values (not used in analysis – *t* &*p* value not reported)

Although groups did not differ in duration or onset of diabetes, the HSR group had higher microvascular disease, $t(28)=-3.65$, $p<.01$, $r=.57$), and higher mean HbA1c, $t(28)=-3.07$, $p<.05$, $r=.50$) than the LSR group. Groups did not differ on insulin resistance, which primarily relies on general health variables (presence of hypertension

and waist-hip-ratio) in calculation of this value. Pearson chi square analysis indicated that groups did not differ on experience of severe hypoglycaemia requiring assistance ($\chi^2(1)=.136$, $p=.50$). The groups were similar in relation to general health variables (Table 8.5).

Table 8.5 *Comparison of General Health Variables by Retinopathy Group*

	LSR (n=15)	**HSR (n=15)**	***t* (28)**	***p***
	$\bar{x}$ (SD)	***$\bar{x}$ (SD)***		
Systolic BP	130.6 (13)	136.7 (13.2)	-1.27	.22
min-max	105-157	120-167		
Diastolic BP	74.6 (10.7)	70.7 (5.99)	1.24	.22
min-max	53-86	59-79		
Waist-Hip Ratio	.877 (.085)	.874 (.099)	.079	.94
min-max	.72-1.0	.73.1.0		
§BMI	1.41_a (.07)	1.46_a (.06)	-1.89	.06
	26.1_b (4.25)	28.9_b (4.01)		
min-max	20.5-33.8	23.1-34.8		
†Total Cholesterol	2.10_a (.16)	2.19_a (.14)	-1.65	.11
	4.42_b (.68)	4.80_b (.61)		
min-max	3.3-5.9	3.7-5.8		
HDL Cholesterol	1.81 (.38)	1.93 (.48)	-.795	.44
min-max	1.2-2.3	1.3-2.96		
§Triglycerides	$-.162_a$ (.19)	$-.077_a$ (.15)	-1.37	.18
	$.769_b$ (.47)	$.884_b$ (.30)		
min-max	.43-2.3	.47-1.6		

*$p<.05$, 2-tailed significance reported.

† Total Cholesterol was transformed for analysis (Square Root).

§ The variable BMI, Triglycerides, and Cholesterol Ratio were transformed for analysis (log 10)

For all transformations, both transformed and non-transformed means are provided

a. Values for reverse square root, with *t* & *p* value

b. Original, untransformed values (not used in analysis – *t* &*p* value not reported)

The LSR and HSR groups were also compared on their performance on cognitive tests shown in Table 8.6. In this small group, there is no significant difference between scores on the cognitive tests for the LSR compared to the HSR group. Groups were also compared on the Ravens Total score using non-parametric Mann-Whitney U test. There was no significant difference on Ravens score between the LSR group (*Mdn*= 44) and HSR groups (*Mdn*= 41), *U=89.0, p*=.35, one-tailed. Differences in brain function identified should not be due to difference in basic cognitive performance between groups.

Table 8.6 *Performance on Cognitive Tests by Retinopathy Group*

	LSR (n=15) $\bar{x}$ **(SD)**	**HSR (n=15)** $\bar{x}$ **(SD)**	***t* (28)**	***p***
§A-ELCC	.274 (.66)	.041 (.99)	.757	.46
†TMT-A	1.20_a (.26)	1.21_a (.37)	-.106	.92
	$-.594_b$ (.65)	$-.499_b$ (.82)		
†TMT-B	1.08_a (.39)	1.17_a (.58)	-.501	.61
	$-.497_b$ (.67)	$-.082_b$ (1.74)		
Story Recall Immed.	.130 (.69)	.180 (.67)	-.201	.84
Story Recall Delay	.177 (.72)	.215 (.67)	-.149	.88
Digit Span	1.37_a (.38)	1.46_a (.36)	-.621	.54
	$.245_b$ (1.1)	$.467_b$ (1.1)		
Symbol Digit (W)	-.085 (.857)	.069 (1.1)	-.424	.68
Symbol Digit (O)	.198 (.99)	.422 (.83)	-.675	.50

2-tailed significance reported.
§A-ELCC=Age-Adjusted Estimate of Lifetime Cognitive Change
TMT=Trail Making Test, lower scores indicate better performance.
†TMT tests and Digit Span were transformed for analysis due to non-normal distribution (Square Root). Both transformed and non-transformed means are provided for ease of understanding.
a. Values for reverse square root, with *t* & *p* value
b. Original, untransformed values (not used in analysis – *t* &*p* value not reported)

8.6.2. Results

N-back

Of the 30 participants who took part in the fMRI scanning, not all were included in the analysis of the working memory test. Two participants from the LSR group and 1 participant from the HSR group

scored below chance on the 2-Back and were excluded from the random-effects analysis leaving 13 participants in the LSR group and 14 in the HSR group.

N-back Behavioural Results

To determine whether the participants experienced greater difficulty on the 2-back version than the 0-back version of the task, performance was compared for the hard and easy versions of the task. As expected, results of paired *t*-test showed that participants performed more accurately and quickly on the 0-back task when the working memory load was low than the 2-back task when the working memory load was high (Table 8.7). Results of Spearman's rho correlation indicated that accuracy on the 0-back was not correlated with response time on the 0-back (r_s=-.163, p=.42). In contrast, accuracy on the 2-back was negatively correlated with response time on the 2-back (r_s=-.770, p<.001) and 0-back (r_s=.391, p<.05). Therefore those with greater response time had less accurate responses.

Table 8.7 *Results of Paired t-Test of Group Performance on 0-Back vs 2-Back Task*

	0 Back	**2 Back**	**t (26)**	***p* *2-tailed***
# Correct	53.52 (2.5)	42.41 (6.0)	-12.37*	.000
Response Time	528.27 (73.4)	770.91 (106.8)	10.26*	.000

Results of *t*-test comparison of the LSR and HSR group on the n-back task are provided in Table 8.8. On the 0-back task, there was no difference between the LSR and HSR group on the number correct and no difference in the response time. On the 2-back task, the LSR group performed more slowly on the 2-back task than the HSR group, $t(25)=2.135$, $p<.05$, two-tailed. Despite taking longer to respond, the LSR group performed no better than the HSR group on the 2-back task.

Table 8.8 *Accuracy and Response Time on N-Back Task for Low Severity Compared with High Severity Retinopathy Group*

N-Back	**Measure**	**LSR (n=13) Mean (SD)**	**HSR (n=14) Mean (SD)**	***t (25)***	***p* *2-tailed***
0	# Correct	53.9 (0.3)	53.3 (0.9)	.494	.62
	RT *ms*	514.7 (16.5)	545.2 (23.4)	-1.26	.22
2	# Correct	40.9 (1.8)	43.9 (1.5)	-1.39	.18
	RT *ms*	815.3(33.5)	731.2 (25.8)	2.14	.02

RT=Response Time in ms *$p<.05$

Whole Group Results

To determine the regions of activation and deactivation on the n-back task, a whole group analysis was completed to determine BOLD activity with increasing task difficulty on the n-back task. Significant clusters at $p<.001$, uncorrected, 5 voxel extent are reported along with the MNI coordinates. Activations that were greater in the hard task (2-back) than the easy task (0-back) are provided in Table 8.9.Significant activations were identified in bilateral frontal areas including a large area surrounding the middle frontal gyrus (~BA 6), left inferior frontal gyrus (~BA 11), and medial frontal gyrus (~BA 6). Areas in the occipital lobe showed activation including the right inferior occipital and left middle occipital (~BA 18), as well as the left cuneus (~BA 17). Significant activation was shown in the superior temporal gyrus (~BA 13) in the temporal lobe and the postcentral gyrus (~BA 3) in the parietal lobe.

Table 8.9 *Activations for the Whole Group with Increasing Task Difficulty on the N-back Task*

Region	Lat	BA	MNI (x,y,z)			Vox.	Z score
			x	y	z		
Frontal							
Middle Frontal Gyrus	R	6	32	12	52	79812	7.35
Inferior Frontal Gyrus	L	11	-14	42	-20	9	3.93
Medial Frontal Gyrus	R	6	18	-20	52	11	3.35
	L	6	-6	-12	72	13	3.30
Occipital							
Inferior Occipital Gyrus	R	18	42	-86	-12	30	3.61
Cuneus	L	17	-16	-90	8	22	3.56
Middle Occipital Gyrus	L	18	-36	-90	0	6	3.19
Temporal							
Superior Temporal Gyrus	R	13	52	-44	20	24	3.58
Parietal							
Postcentral Gyrus	L	3	-36	-36	66	17	3.45

SPM clusters containing at least 5 significant voxels (p <001, uncorrected). MNI coordinates (x,y,z) refer to cluster maxima reported in MNI space. Lat.= laterality; BA= approximate Brodmann's area; Vox.= number of significant voxels

Significant deactivations, $p<.001$, 5 voxel extent were identified for the whole group on the hard version of the task (2-back) greater than the easy version of the task (0-back). MNI coordinates of cluster maxima are provided in Table 8.10. Significant deactivations were identified in the left medial prefrontal cortex and several areas of the temporal lobe including the left middle temporal gyrus (~BA 21 & 39) and bilateral superior temporal gyrus (~BA 22/38/41). In the posterior region, significant deactivation was identified in the left precuneus

(~BA 31) of the parietal lobe. Sub-lobar areas were also deactivated including bilateral insula (~BA 13), and claustrum.

Table 8.10 *Deactivations for the Whole Group with Increasing Task Difficulty on the N-back Task*

Region	Lat	BA	MNI (x,y,z)			Vox.	Z score
			x	y	z		
Frontal							
Medial Frontal Gyrus	L	-	-10	50	2	936	4.83
Temporal							
Middle Temporal Gyrus	L	21	-48	2	-36	123	4.84
	L	39	-52	-74	26	10	3.65
Superior Temporal Gyrus	L	38	-34	2	-24	17	4.10
	R	22	56	-2	4	8	3.46
	L	41	-48	-28	16	8	3.46
Parietal							
Precuneus	L	31	-8	-56	32	564	5.04
Sub-Lobar							
Insula	L	13	-42	-16	-8	45	4.04
	R	13	48	-26	20	48	4.03
	L	13	-40	-14	12	76	3.76
Claustrum	R	-	36	8	8	6	3.64

Listed regions are SPM clusters containing at least 5 significant voxels ($p < 001$, uncorrected). MNI coordinates (x,y,z) refer to cluster maxima reported in MNI space. Lat.= laterality; BA= approximate Brodmann's location; Vox. = number of significant voxels;

The images for the whole group results on activation and deactivation associated with increasing task difficulty are shown in

Figure 8.3. Large areas of activation can be seen in the frontal, parietal lobes, and cerebellum. Deactivation was focused in the medial frontal regions and temporal areas.

a b

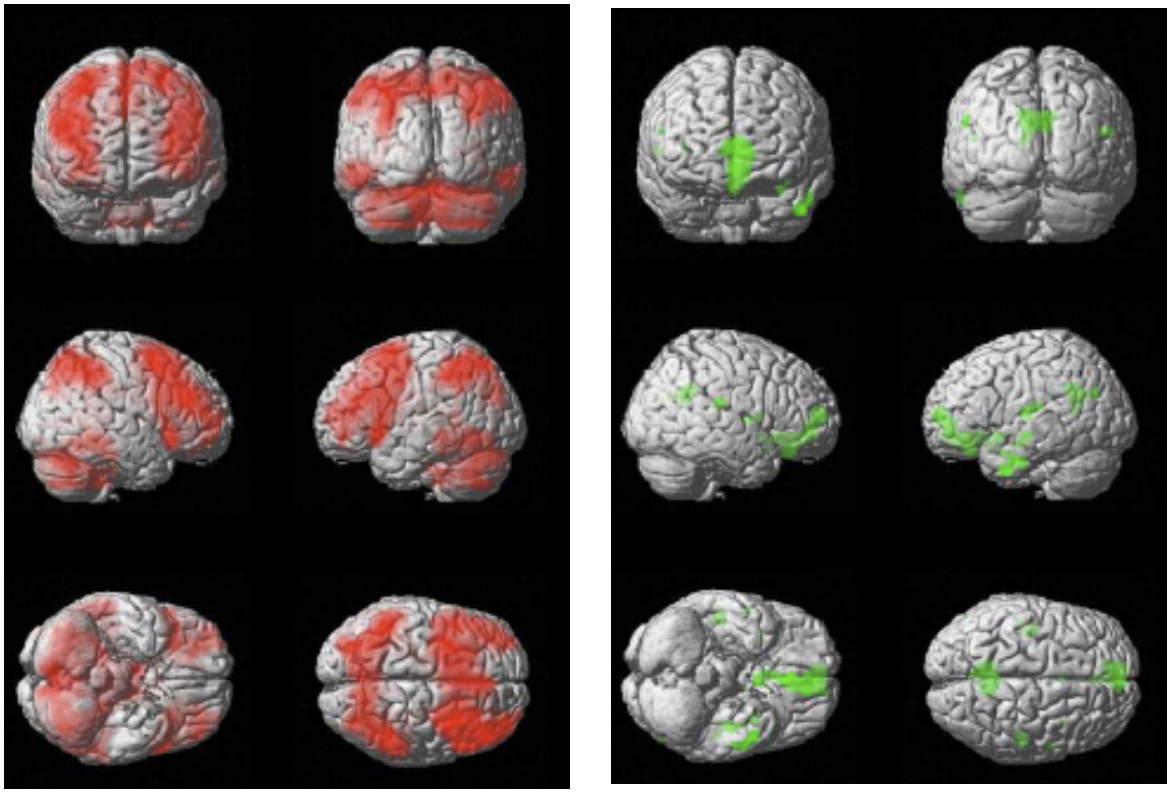

Figure 8.3 Image of results for the whole group n-back (a) activations and (b) deactivations with increased task difficulty (2-back >0-back), threshold $p<.001$ *unc*, 5 voxel extent

Retinopathy group comparison

Random-effects analysis was performed to compare the HSR and LSR group in relation to activation on the hard (2-back) in comparison to the easy (0-back) version of the n-back task. If there are signs of accelerated ageing in the BOLD activation for the HSR group should be comparable to findings from functional ageing research including greater frontal activity and less DMN deactivation in comparison to the LSR group.

There were no significant activations for the LSR group over the HSR group with increasing task difficulty at the significance level of $p<.001$,unc, 5 voxel extent. When comparing activations that are greater in the Hard (2-back) than the Easy (0-back) task, the HSR group showed significant differences in activations. MNI coordinates of cluster maximum derived from the analysis are displayed in Table 8.11.

Table 8.11 *Activations for the HSR Group > LSR Group with Increasing Task Difficulty on the N-back Task*

Region	Lat	BA	MNI (x,y,z)			Vox.	Z score
			x	y	z		
Frontal							
Middle Frontal Gyrus	L	11	-22	30	-14	44	4.18
	L	9	-12	46	30	29	3.93
	L	10	-6	58	14	88	3.83
	R	9	10	54	24	16	3.76
	R	10	6	56	12	7	3.40
Superior Frontal Gyrus	L	11	-10	52	-16	14	3.57
Temporal							
Inferior Temporal Gyrus	L	20	-56	-32	-22	12	4.01
Parietal							
Precuneus	L	31	-8	-56	32	8	3.45
Limbic							
Anterior Cingulate	L	32	-8	36	18	36	3.83
	L	32	-10	36	-12	20	3.70
Posterior Cingulate	L	29	-6	-46	10	5	3.23
Cerebellum							
Uvula	L	-	-20	-86	-36	37	3.66

Listed regions are SPM clusters containing at least 5 significant voxels ($p < 001$, uncorrected). MNI coordinates (x,y,z) refer to cluster maxima reported in MNI space. Lat.= laterality; BA= approximate Brodmann's location; Vox. = number of significant voxels;

The HSR group showed higher activation in several frontal areas including bilateral areas in the middle frontal gyrus (~BA 9/10/11) and

the superior frontal gyrus (~BA 11). Activations were also higher for the HSR group than the LSR group on the hard version (2-back) of the task in the inferior temporal gyrus (~BA 20) and the precuneus (~BA 31) in the parietal lobe. Areas in the cingulate cortex also showed higher activation for the HSR group on this task including the left anterior cingulate cortex (~BA 32) and posterior cingulate cortex (~BA 29) along with a region in the cerebellum.

It is possible that the significant difference identified in activation between the LSR and HSR group could be due to activation that is relatively higher in one group than the other, deactivation that is relatively less in one group than the other, or activation in one group and deactivation in the other. The cluster maxima were converted to a region of interest directly from the SPM output. Using the MarsBaR toolbox (Brett et al., 2002), beta values were extracted for each of these regions to determine the reason for the difference between the LSR and HSR group in these particular regions. Beta values are the estimated response amplitude difference between the 2-back and 0-back tasks. A positive value therefore indicates activation and a negative value indicates deactivation. Figure 8.4 displays the beta values extracted from the significant areas determined in the statistical analysis.

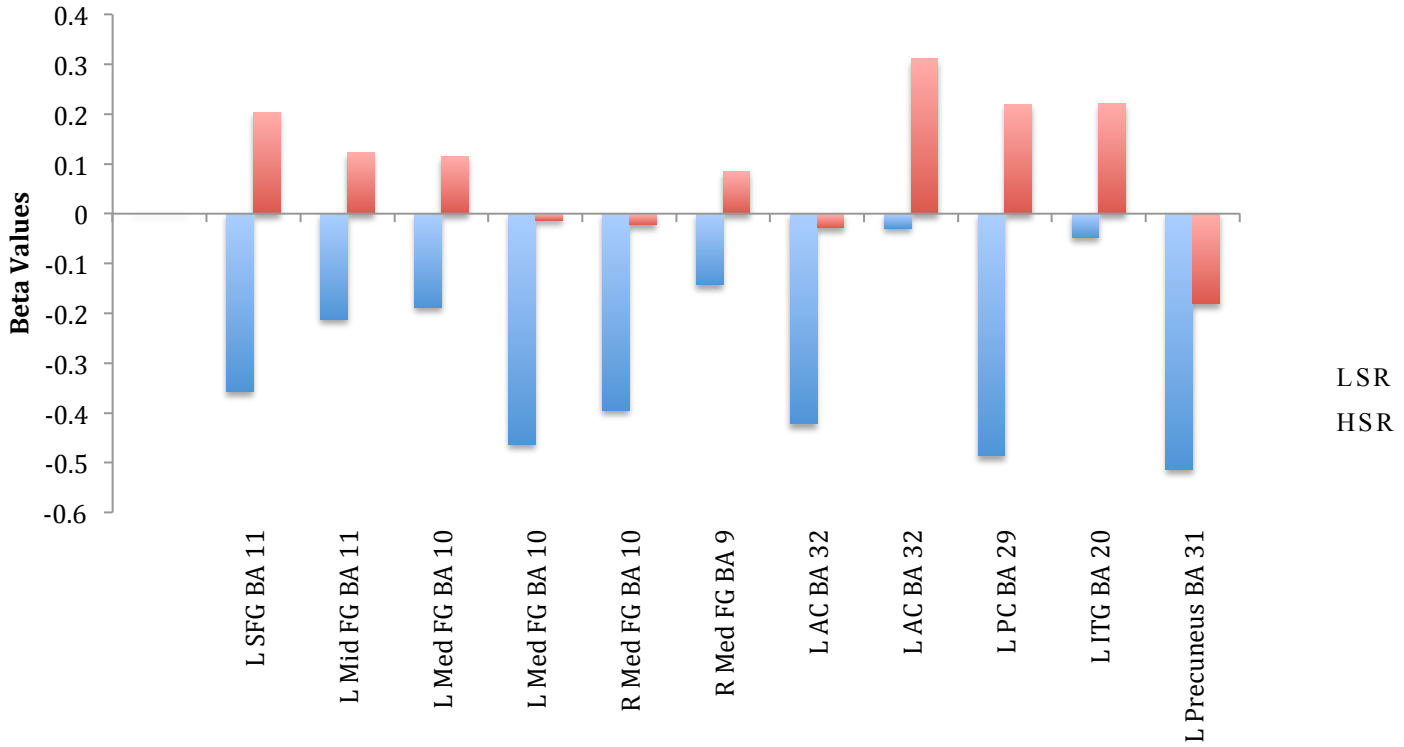

Figure 8.4 Beta values for significant activations HSR>LSR on the 2back working memory task. A negative value indicates deactivation. The line in the middle of the graph denotes the beta value of 0. SFG= superior frontal gyrus; Mid FG=middle frontal gyrus; Med FG=medial frontal gyrus; AC=anterior cingulate; PC=posterior cingulate; ITG=inferior temporal gyrus; L=Left; R=Right; BA=approximate Brodmann's area

Retinopathy Group by Age Comparisons

If retinopathy is influencing accelerated ageing of brain function, then a young group with high severity of retinopathy should show brain function that can be related to a pattern shown in ageing when compared to an older group with low severity of retinopathy. The retinopathy groups were split by age. ANOVA was used to compare the young group without retinopathy and the young group with retinopathy to the older group without retinopathy and the older group with retinopathy for activations greater on the hard versus easy versions of the n-back task. Table 8.12 provides sample size and mean age/SD and age range for the young and old groups with HSR and LSR.

Table 8.12 *Mean Age and Sample Sizes for Retinopathy Groups by Age*

	Young		**Old**	
	LSR	HSR	LSR	HSR
n	6	7	6	8
Mean Age	48.19	48.32	57.49	57.75
(SD)	(2.86)	(2.17)	(3.15)	(3.64)
Age Range	46-52	45-53	55-63	55-61

On the hard versus the easy n-back task, there was a significant main effect of retinopathy and age (t (23), 3.48, p<.001,unc., 5 voxel extent) and a significant interaction between age and retinopathy group F(1,23)=9.63, p<.005. Post Hoc comparison indicated that the young HSR group showed several areas of higher activation than the old LSR

group, $t(23)$, 3.48, $p<.001$, *unc., 5 voxel extent.* MNI coordinates for cluster maxima, are displayed in Table 8.13. To determine the direction of the differences in activation between groups, beta values were extracted for each area in the method described previously and are provided in Figure 8.5. Significant differences in activation for the HSR group greater than the LSR group included bilateral areas across the dorsolateral prefrontal cortex (BA 9), left inferior parietal lobule (BA 40), and right post-central gyrus (BA40). The young HSR group also showed several areas of activations whereas the old LSR group showed deactivations including the areas of BA 9 in the left middle frontal gyrus and left precentral gyrus, the left superior temporal gyrus (BA38), the left middle occipital gyrus (BA 19, 37) and the cerebellum. There were no greater activations for the old LSR group over the young HSR group.

Table 8.13 *Young HSR > Old LSR Group Activation with increasing task difficulty on N-Back Task*

Region	Lat	BA	MNI (x,y,z)			Vox.	Z score
			x	y	z		
Frontal							
Superior Frontal Gyrus	L	9	-16	40	42	23	3.88
Precentral Gyrus	L	9	-36	20	42	9	3.51
Middle Frontal Gyrus	L	9	-34	14	30	7	3.42
	R	9	42	30	40	7	3.27
	L	9	-46	18	34	5	3.25
Inferior Frontal Gyrus	R	9	56	16	26	9	3.42
Occipital							
Lingual Gyrus	L	18	-12	-88	-18	82	4.27
	L	17	-4	-92	-12		3.84
Middle Occipital Gyrus	L	19	-46	-86	-2	9	3.56
	L	37	-54	-74	2	8	3.35
Parietal							
Postcentral Gyrus	R	40	54	-36	56	10	3.79
	L	2	-54	-30	40	24	3.70
Inferior Parietal Lobule	L	40	-52	-38	50	10	3.34
Temporal							
Superior Temporal Gyrus	L	38	-36	24	-24	7	3.26
Limbic							
Anterior Cingulate	L	32	-8	36	18	8	3.68
Cerebellum							
Declive	L	-	-44	-70	-24	6	3.37

Listed regions are SPM clusters containing at least 5 significant voxels ($p < 001$, unc). MNI coordinates (x,y,z) refer to cluster maxima reported in MNI space. Lat.= laterality; BA= approximate Brodmann's area; Vox. = number of significant voxels

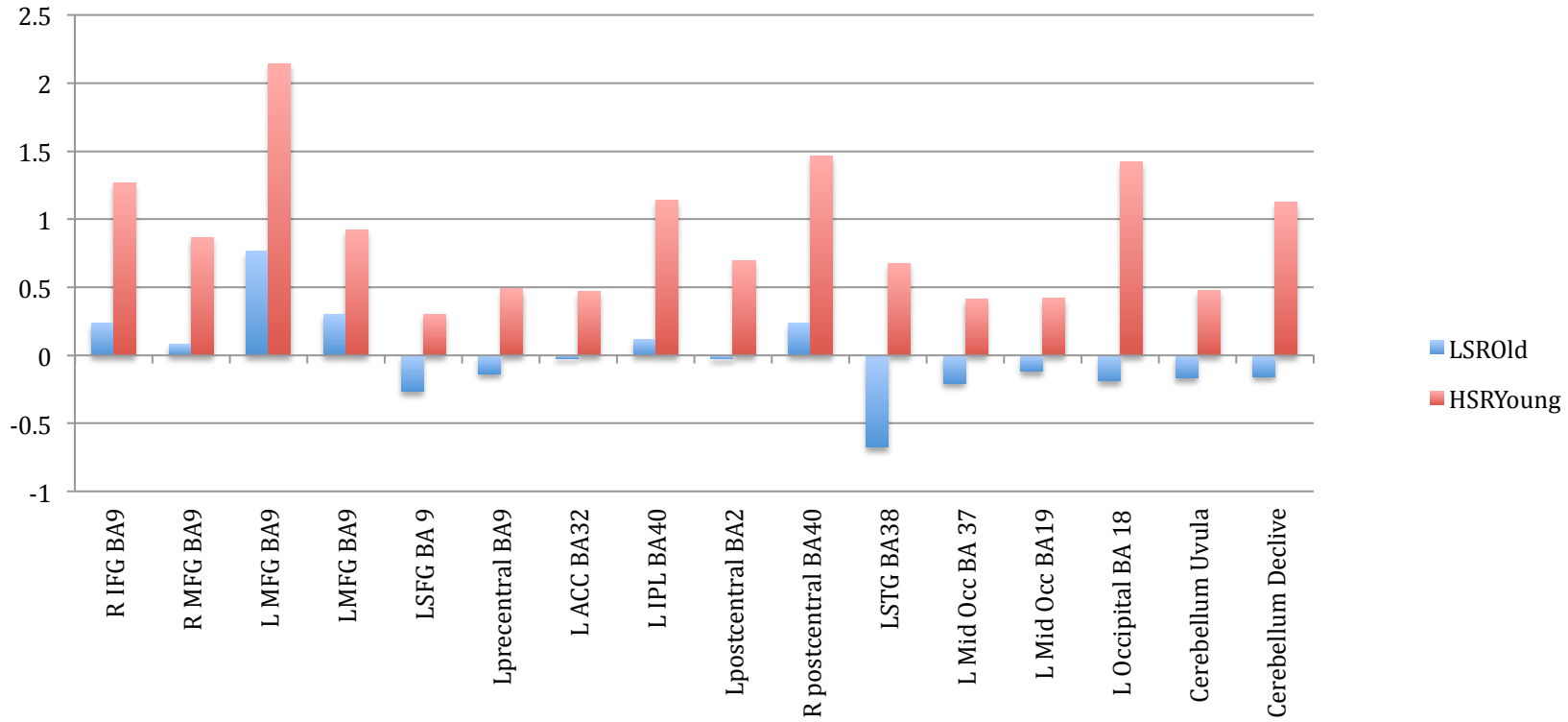

Figure 8.5 Beta values for significant activations Young HSR> Old LSR with increasing task difficulty on the n-Back task

8.6.3. Resting State: Functional Connectivity Analysis

The hippocampal-cortical memory system (HCMS) identified by Vincent and colleagues (2008) is a part of the default-mode network, is active during passive mental states, and is internally directed. Regions in this system include the ventral medial PFC (vmPFC), posterior inferior parietal lobule, retrosplenial cortex, posterior cingulate and lateral temporal lobe. The vmPFC (Brodmann's Area 10) was chosen as a seed ROI for resting state analysis given that this area was highlighted in differences between the group with and without retinopathy. Resting state functional activity analysis can provide information on whether functional connectivity for the HSR group, and not the LSR group, is consistent with research on the DMN in ageing. This finding would provide evidence of accelerated ageing in the HSR group.

Whole Group Results: Ventromedial Prefrontal Cortex Seed Region

MNI coordinates and regions for clusters that show activation that is positively correlated with activation in the ventromedial prefrontal cortex (vmPFC) seed (x=0,y=51,z=-7) for the whole group is provided in Table 8.14. Activity in the vmPFC seed was positively correlated with activity in a large area surrounding the seed (~BA 10) and in the bilateral inferior (~BA 47), and left superior (~BA 6) frontal lobe. Large areas were also positively correlated with the vmPFC seed in the left precuneus (~BA 31), several areas of the temporal lobe (~BA 20/21/38/39), bilaterally in the parahippocampal

gyrus (~BA 28), the left anterior cingulate (~BA 32), and caudate area of the basal ganglia. Several areas of the cerebellum were also positively correlated with activation in this seed.

Table 8.14 *Functional Connectivity for Whole Group: Regions Demonstrating Positive Correlation with Ventral Medial Seed Region*

Region	Lat	BA	MNI (x,y,z)			Vox.	Z score
			x	y	z		
Frontal							
Medial Frontal Gyrus	R	10	2	48	-6	10001	65535
Inferior Frontal Gyrus	R	47	32	30	-18	155	5.65
	R	47	30	16	-18	37	4.08
	L	47	-36	34	-12	8	3.66
	L	47	-24	12	-16	6	3.54
Sup. Frontal Gyrus	L	6	-10	26	62	6	3.55
Occipital							
Precuneus	L	31	-2	-68	26	4717	6.56
Temporal							
Inferior Temporal Gyrus	L	20	-60	-10	-26	1021	5.70
Fusiform Gyrus	R	20	58	-6	-28	423	5.80
Angular Gyrus	L	39	-54	-70	32	944	6.01
Sup. Temporal Gyrus	R	39	56	-62	26	835	5.87
	R	38	32	20	-38	122	4.56
Middle Temporal Gyrus	R	21	66	-20	-16	9	3.37
Limbic							
Parahippocampal Gyrus	L	28	-24	-18	-20	565	5.48
	R	28	24	-20	-20	313	5.24
Anterior Cingulate	L	32	-6	34	28	13	3.45

Table 8.14 (cont.)

Region	Lat	BA	MNI (x,y,z)			Vox.	Z score
			x	y	z		
Basal Ganglia							
Caudate	L	-	-14	20	6	5	3.42
Cerebellum							
Declive	L	-	-26	-90	-30	91	4.89
Cerebellar Tonsil	R	-	8	-48	-50	331	4.81
Pyramis	R	-	12	-90	-40	92	4.45
Tuber	R	-	50	-66	-40	109	4.03
	L	-	-34	-80	-38	6	3.31

Listed regions are SPM clusters containing at least 5 significant voxels ($p < 001$, uncorrected. MNI coordinates (x,y,z) refer to cluster maxima reported in MNI space. Lat.= laterality; BA= approximate Brodmann's location; Vox. = number of significant voxels; Sup.=superior

MNI coordinates and regions for clusters that show activation that is negatively correlated with activation in the vmPFC seed (x=0,y=51,z=-7) for the whole group are indicated in Table 8.15. Negative correlations were found in the right inferior frontal (~BA 44), bilateral middle frontal (~BA 46), superior frontal (~BA 6), and bilateral precentral (~BA 6/9) gyri as well as a right sub-gyral area (~BA 10) in the frontal lobe. Areas of the left occipital lobe (~BA 18/19), temporal lobe (~BA 19/37), parietal lobe (~BA 2/7/40), cingulate gyrus (~BA 30/31) were also indicated. Sub-lobar, brainstem and the cerebellum also showed negative correlation to the seed ROI activation.

Table 8.15 *Functional Connectivity for Whole Group: Regions Demonstrating Negative Correlation with Ventral Medial Seed Region*

Region	Lat	BA	MNI (x,y,z)			Vox.	Z score
			x	y	z		
Frontal							
Inferior Frontal Gyrus	R	44	54	16	12	2252	5.79
Middle Frontal Gyrus	L	46	-46	38	26	1129	6.32
	R	46	40	48	20	263	4.68
	R	6	38	-2	48	7	3.83
	R	6	48	6	50	32	3.69
Precentral Gyrus	L	6	-52	-6	28	11	3.59
Precentral Gyrus	R	9	36	6	36	12	3.58
Occipital							
Middle Occipital Gyrus	L	19	-54	-68	-12	659	6.01
	L	19	-36	-88	14	28	3.71
Lingual Gyrus	L	18	-16	-78	0	361	4.91
Cuneus	L	18	-2	-82	10	18	3.36
Temporal							
Middle Temporal Gyrus	R	37	56	-62	-6	123	4.93
	R	19	42	-78	18	105	4.53
Fusiform Gyrus	L	37	-48	-50	-20	9	3.41
Parietal							
Inferior Parietal Lobule	L	40	-60	-36	44	11480	7.39
Postcentral Gyrus	R	2	60	-32	42	4336	6.49
	L	7	-20	-52	72	7	3.60
Limbic							
Cingulate Gyrus	L	31	-12	-30	38	56	4.62
	R	31	16	-32	42	52	3.82
Posterior Cingulate	R	30	18	-70	4	213	4.21

Table 8.15 (cont.)

Region	Lat	BA	MNI (x,y,z)			Vox.	Z score
			x	y	z		
Sub-Lobar							
Claustrum	R	-	36	-2	10	38	4.23
Thalamus	R	-	10	-22	-2	15	3.81
	L	-	-20	-10	12	5	3.36
Lentiform Nucleus	L	-	-14	2	4	7	3.50
Insula	R	13	40	-16	-12	13	3.39
Insula	R	13	44	-38	18	7	3.31
Midbrain							
Brainstem	L	-	-4	-28	-10	7	3.36
Cerebellum							
Declive	L	-	-30	-60	-28	347	5.15
	R	-	26	-68	-24	407	5.06
Inf. Semi-Lunar Lobule	R	-	22	-74	-50	107	5.07
Inf. Semi-Lunar Lobule	L	-	-20	-72	-50	60	4.31
Tuber	L	-	-42	-58	-34	73	4.39
	R	-	48	-56	-32	7	3.72
Cerebellar Tonsil	L	-	-34	-56	-48	8	3.76
Culmen	L	-	-36	-44	-36	12	3.61

Listed regions are SPM clusters containing at least 5 significant voxels ($p < 001$, uncorrected. MNI coordinates (x,y,z) refer to cluster maxima reported in MNI space. Lat.= laterality; BA= approximate Brodmann's location; Vox. = number of significant voxels; Inf=inferior

Retinopathy Group Results Ventromedial Seed Region

Results were analyzed separately for the HSR and LSR groups to determine whether there were noticeable differences in the positive and negatively correlated activations for one or both of these groups in comparison to the pattern for the whole group. Less connectivity for the HSR group than the LSR or whole group would provide evidence of accelerated ageing in this group. Areas with positive correlation to activation in the vmPFC seed ROI for the LSR group are indicated in Table 8.16. The LSR group showed a similar pattern of positive correlation with activation in the ventromedial PFC seed to the whole group including a large area surrounding the seed in the right medial frontal gyrus (~BA 10), bilateral inferior frontal gyrus (~BA 47), left precentral gyrus (~BA 6) and right superior frontal gyrus (~BA 18), and similar bilateral regions as the whole group in the temporal lobe (~BA 21/38/39). A positive correlation was also seen for activation in bilateral parahippocampal gyrus (~BA 28/30/35) and right cingulate (~BA 18), bilateral thalamus, right caudate and bilateral areas of the cerebellum, also identified in the whole group analysis. Areas near the hippocampus (BA 28), vmPFC (BA 10) and lateral temporal lobe (BA 39) are positively associated with the HCMS, active in rest.

Table 8.16 *Functional Connectivity for LSR Group: Regions Demonstrating Positive Correlation with Ventral Medial Seed Region*

Region	Lat	BA	MNI (x,y,z)			Vox.	Z score
			x	y	z		
Frontal							
Medial Frontal Gyrus	R	10	12	54	-2	7407	6.33
Inf. Frontal Gyrus	R	47	32	30	-18	47	4.28
	R	47	24	14	-24	13	3.57
	L	47	-24	10	-16	5	3.66
Precentral Gyrus	L	6	-36	-22	70	8	3.55
Superior Frontal Gyrus	R	8	10	46	46	6	3.69
Temporal							
Sup. Temporal Gyrus	R	39	56	-60	26	718	4.76
	L	38	-40	18	-38	57	4.51
	R	38	30	18	-36	9	3.64
	L	38	-30	8	-32	15	3.58
Inf. Temporal Gyrus	R	21	62	-4	-24	296	5.56
Middle Temporal Gyrus	L	21	-64	-14	-18	293	4.98
Angular Gyrus	L	39	-54	-70	32	588	4.96
Limbic							
Cingulate Gyrus	R	31	4	-52	26	3847	5.86
Parahippocampal Gyrus	L	35	-28	-20	-24	434	5.07
	R	28	24	-16	-26	209	4.49
	L	28	-16	-8	-16	8	3.86
	L	30	-14	-38	-8	15	3.73
	L		-26	-6	-14	10	3.73
Sub-lobar							
Thalamus	L	-	-2	-14	6	41	4.27
	R	-	2	-2	8	10	3.75

Table 8.16 (cont.)

Region	Lat	BA	MNI (x,y,z)			Vox.	Z score
			x	y	z		
Basal Ganglia							
Caudate	R		16	20	10	10	3.60
Cerebellum							
Cerebellar Tonsil	L	*	-4	-56	-46	159	4.57
Uvula	R	-	22	-92	-34	22	4.18
Tuber	L	-	-20	-88	-42	53	3.67

Listed regions are SPM clusters containing at least 5 significant voxels ($p < 001$, uncorrected. MNI coordinates (x,y,z) refer to cluster maxima reported in MNI space. Lat.= laterality; BA= approximate Brodmann's location; Vox. = number of significant voxels; Inf=inferior; Sup=Superior

For the HSR group, activations that were positively correlated with activity in the vmPFC seed ROI (shown in Table 8.17) included a large area in the right medial frontal gyrus surrounding the seed (~BA 10), right inferior part of the medial frontal gyrus (~BA 25), right middle frontal gyrus (~BA 11), and bilateral inferior frontal gyrus (~BA 47). Activations also included the right cuneus (~BA 17), several areas bilaterally in the temporal gyrus (~BA 20/21/38/39), left inferior parietal lobule (~BA 39), right posterior cingulate (~BA 30), bilateral anterior cingulate (~BA 24/25), bilateral parahippocampal gyrus (~BA 28/37) and several areas of the cerebellum.

Table 8.17 *Functional Connectivity for HSR Group: Regions Demonstrating Positive Correlation with Ventral Medial Seed Region*

Region	Lat	BA	MNI (x,y,z)			Vox.	Z score
			x	y	z		
Frontal							
Medial Frontal Gyrus	R	10	2	48	-8	3659	7.26
	R	25	2	20	-18	10	4.76
Middle Frontal Gyrus	R	11	32	36	-18	59	4.49
Inferior Frontal Gyrus	L	47	-32	30	-14	50	4.33
	L	47	-40	22	-18	22	3.66
	R	47	28	12	-18	9	3.47
Occipital							
Cuneus	R	17	12	102	0	9	3.43
Temporal							
Middle Temporal Gyrus	L	21	-56	-10	-22	163	4.73
	L	21	-46	10	-40	25	4.02
	R	39	56	-68	28	82	3.94
	R	21	58	4	-26	35	3.87
	R	38	44	12	-46	20	3.75
	L	21	-50	8	-32	5	3.42
Sup. Temporal Gyrus	L	38	-36	16	-28	38	4.45
	R	38	44	22	-26	6	3.31
	R	38	34	22	-38	22	3.30
Inferior Temporal Gyrus	L	20	-52	-2	-40	8	3.65
	R	20	50	-12	-32	5	3.50
Parietal							
Inferior Parietal Lobule	L	39	-46	-72	40	278	4.44
Limbic							
Posterior Cingulate	R	30	6	-52	16	1701	5.07

Table 8.17 (cont.)

Region	Lat	BA	MNI (x,y,z)			Vox.	Z score
			x	y	z		
Anterior Cingulate	L	25	-2	2	-10	19	3.83
	L	25	-6	10	-10	12	3.82
	R	25	4	12	-8	35	3.68
	R	24	8	28	16	12	3.33
Parahippocampal Gyrus	R	37	36	-38	-10	25	4.47
	L	28	-22	-18	-22	13	3.53
	R	28	22	-26	-14	5	3.50
Sub-Lobar							
Hypothalamus	R	-	10	-6	-14	36	3.82
Basal Ganglia							
Caudate	R	-	14	16	12	15	3.79
	L	-	-14	18	4	5	3.39
	R	-	14	26	4	10	3.39
Amygdala	L	-	-22	-8	-16	12	3.68
Cerebellum							
Declive	L	-	-28	-88	-30	23	4.17
Cerebellar Tonsil	L	-	14	-50	-44	65	4.15
Uvula	R	-	26	-82	-34	45	3.61
Pyramis	L	-	-10	-86	-42	6	3.34
	R	-	38	-76	-44	5	3.24

Listed regions are SPM clusters containing at least 5 significant voxels ($p < 001$, uncorrected. MNI coordinates (x,y,z) refer to cluster maxima reported in MNI space. Lat.= laterality; BA= approximate Brodmann's location; Vox. = number of significant voxels; Sup.=superior.

The HSR group showed similar regions of positive correlation with activation in the ventromedial PFC to the whole group and LSR group, however the activation was not as extensive within each particular region (smaller voxel extent with many areas under 10 voxels) and was present across more areas. This can be seen when the images of positively correlated activations are combined in Figure 8.6. The figure shows the green areas (LSR) surrounding smaller yellow areas (LSR & HSR) showing combined centres of activation illustrating the larger extent of activation for the LSR group. Small red areas, indicate activity outside these common centres of activation particular to the HSR group.

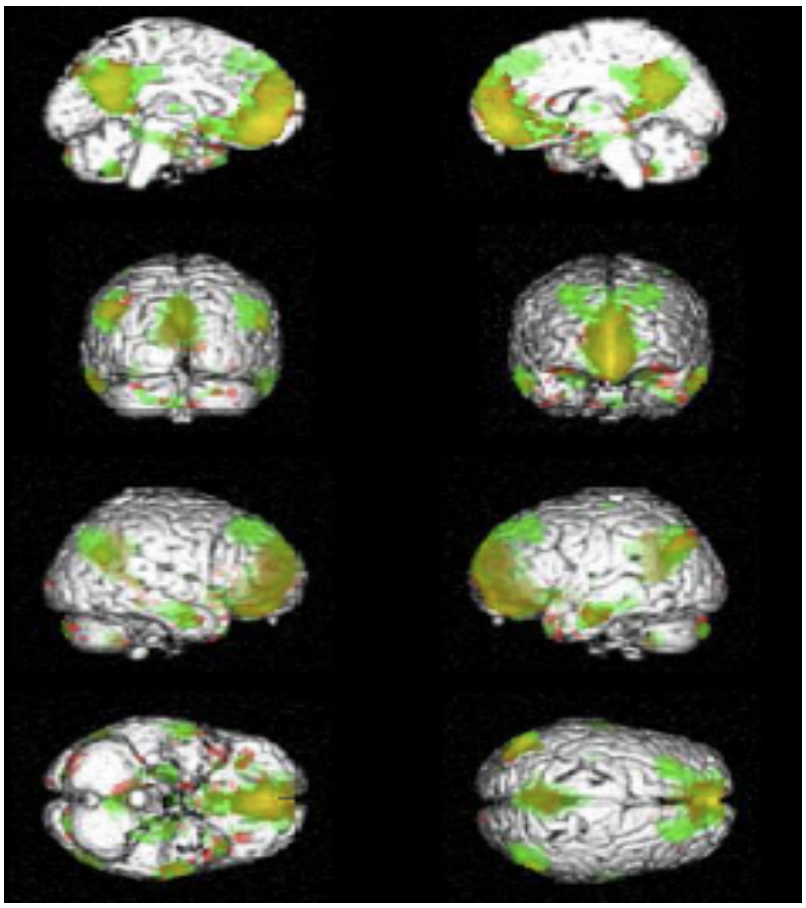

Figure 8.6 Combined activation for LSR (green) and HSR (red) group positively correlated with activation in the ventromedial seed region. Yellow regions indicate combined areas of activation

For the LSR group, activations that were negatively correlated with activity in the vmPFC seed ROI (shown in Table 8.18) included the precentral gyrus (~BA 6/44), middle frontal (~BA 6/10/46), superior frontal (~BA 6), and inferior frontal gyri (~BA 9/47) in the frontal lobe. Other areas included areas such as bilateral middle occipital gyri (~BA 19) and left lingual gyrus and left cuneus (~BA 18) in the occipital lobe. Areas in the temporal lobe included bilateral superior temporal gyrus (~BA 22) and the postcentral gyrus (~BA 2/3/7). The inferior parietal lobule (~BA 40), bilateral cingulate cortex (~BA 24/30/31), sub-lobar areas and regions of the cerebellum were also negatively correlated with activation in the seed region in the LSR group.

Table 8.18 *Functional Connectivity for LSR Group: Regions Demonstrating Negative Correlation with Ventral Medial Seed Region*

Region	Lat	BA	MNI (x,y,z)			Vox.	Z score
			x	y	z		
Frontal							
Precentral Gyrus	L	44	-48	10	12	1995	4.98
	L	6	-44	-16	30	44	3.97
Middle Frontal Gyrus	L	46	-46	36	26	1025	5.64
	R	10	46	48	-4	159	4.25
	R	10	32	56	10	98	4.11
	R	6	40	0	44	13	3.93
	R	6	48	4	50	26	3.91
	L	6	2	14	50	442	4.79
Superior Frontal Gyrus	R	6	26	6	60	152	4.62
	L	6	-10	-10	72	21	3.86

Table 8.18 (cont.)

Region	Lat	BA	MNI (x,y,z)			Vox.	Z score
			x	y	z		
Inferior Frontal Gyrus	R	9	50	6	36	25	3.64
	R	9	44	10	24	18	3.55
	L	47	-32	24	-10	5	3.40
Occipital							
Middle Occipital Gyrus	L	19	-54	-64	-12	268	4.88
	R	19	38	-78	16	45	4.23
Lingual Gyrus	L	18	-16	-76	0	80	3.78
Cuneus	R	18	10	-76	14	28	3.94
Temporal							
Superior Temporal Gyrus	R	22	54	8	4	1227	5.65
	L	22	-56	-12	8	59	4.05
Parietal							
Inferior Parietal Lobule	L	40	-40	-46	46	3051	5.92
Postcentral Gyrus	R	2	58	-30	44	2233	5.79
	L	7	-20	-52	70	7	3.72
	R	3	32	-36	70	5	3.72
Limbic							
Cingulate Gyrus	R	31	14	-24	40	18	3.52
	L	24	-10	6	36	17	3.86
	L	31	-14	-28	38	8	3.42
	R	24	8	-4	46	6	3.79
	R	24	8	8	36	10	3.63
Posterior Cingulate	R	30	20	-68	6	19	3.68
Sub-Lobar							
Claustrum	R	-	36	-16	-6	5	3.21

Table 8.18 (cont.)

Region	Lat	BA	MNI (x,y,z)			Vox.	Z score
			x	y	z		
Midbrain							
Red Nucleus	L	-	-6	-20	-12	6	3.48
Cerebellum							
Declive	R	-	26	-68	-24	162	5.62
	R	-	8	-78	-24	124	4.31
	L	-	-16	-58	-22	19	3.86
	R	-	10	-62	-18	13	3.48
Pyramis	L	-	-10	-76	-38	77	4.08
Culmen	L	-	-40	-50	-32	471	4.77
	R	-	36	-56	-32	78	4.88
	L	-	-4	-66	-6	9	3.43
Inf. Semi-Lunar Lobule	R	-	22	-72	-50	58	3.92

Listed regions are SPM clusters containing at least 5 significant voxels ($p < 001$, uncorrected. MNI coordinates (x,y,z) refer to cluster maxima reported in MNI space. Lat.= laterality; BA= approximate Brodmann's location; Vox. = number of significant voxels.

For the HSR group, activations that were negatively correlated with activity in the vmPFC seed ROI (shown in Table 8.19) included the precentral gyrus (~BA 6), middle frontal (~BA 6/46), superior frontal (~BA 6/9), and inferior frontal gyri (~BA 9/46). Other areas included those in the occipital region including the bilateral middle occipital gyri (~BA 19), left cuneus (~BA 17/18), and right precuneus (~BA 31).

Table 8.19 *Functional Connectivity for HSR Group: Regions Demonstrating Negative Correlation with Ventral Medial Seed Region*

Region	Lat	BA	MNI (x,y,z)			Vox.	Z score
			x	y	z		
Frontal							
Precentral Gyrus	L	6	-46	4	42	254	4.48
	R	6	32	8	34	27	4.01
	R	6	50	-8	28	8	3.58
Middle Frontal Gyrus	L	46	-44	36	30	105	4.25
	R	6	28	-2	52	17	3.78
	R	6	22	14	62	25	3.57
	R	46	42	48	20	5	3.34
	R	6	40	4	58	5	3.29
Inferior Frontal Gyrus	L	9	-50	14	24	180	4.65
	L	46	-50	38	12	13	3.67
	L	46	-48	48	8	6	3.63
Superior Frontal Gyrus	L	9	-36	36	32	8	3.43
	L	6	-26	6	56	5	3.34
Occipital							
Middle Occipital Gyrus	R	19	56	-64	-10	44	3.94
	R	19	40	-82	8	20	4.01
	L	19	-38	-86	16	7	4.03
Cuneus	L	17	-18	-80	6	34	4.12
	L	18	-4	-82	24	8	3.59
Precuneus	R	31	24	-66	22	10	3.47
Temporal							
Superior Temporal Gyrus	L	39	-52	-54	6	326	4.63
	L	22	-56	8	-4	44	4.37

Table 8.19 (cont.)

Region	Lat	BA	MNI (x,y,z)			Vox.	Z score
			x	y	z		
Superior Temporal Gyrus	L	22	-62	-42	16	26	3.56
	R	22	64	-4	8	14	3.83
	R	22	56	-54	4	12	3.96
	L	22	-60	8	4	9	3.82
	R	22	58	14	-6	6	3.34
Middle Temporal Gyrus	R	39	44	-78	20	7	3.36
Parietal							
Precuneus	R	7	20	-66	44	1610	4.99
	L	7	-8	-76	48	42	4.01
Inferior Parietal Lobule	L	40	-62	-36	44	1918	5.01
Limbic							
Cingulate Gyrus	R	32	10	18	46	674	4.38
	L	31	-14	-32	42	11	3.50
Sub-Lobar							
Insula	R	13	48	10	2	366	5.19
Claustrum	L	-	-34	6	2	48	4.24
	R	-	38	-8	10	19	4.04
Cerebellum							
Declive	L	-	-30	-60	-28	23	4.02
Uvula	R	-	18	-74	-42	8	3.97

Listed regions are SPM clusters containing at least 5 significant voxels ($p < .001$, uncorrected). MNI coordinates (x,y,z) refer to cluster maxima and are reported in MNI space. Lat.= laterality; BA= approximate Brodmann's location; Vox. = number of significant voxels

Negatively correlated activation was also found in the temporal gyrus in regions including the bilateral superior temporal gyrus (~BA 22), and middle/superior temporal gyrus (~BA 39). Other regions included the inferior parietal lobule (~BA 40), precuneus (~BA 7), and bilateral cingulate cortex (~BA 31/32). Sub-lobar areas included the claustrum and insula (~BA 13). Bilateral regions of the cerebellum were also indicated.

Negative correlations were less focused for the HSR group showing in a greater number of activated areas with small extent size. This can be seen when the images of negatively correlated activations are combined in Figure 8.7. The figure shows the green areas (LSR) ranging across wider regions (higher extent values). Small red areas indicate scattered activity outside these common centres of activation particular to the HSR group. Yellow areas indicate sections negatively correlated with activation in the vmPFC for both the LSR and HSR groups.

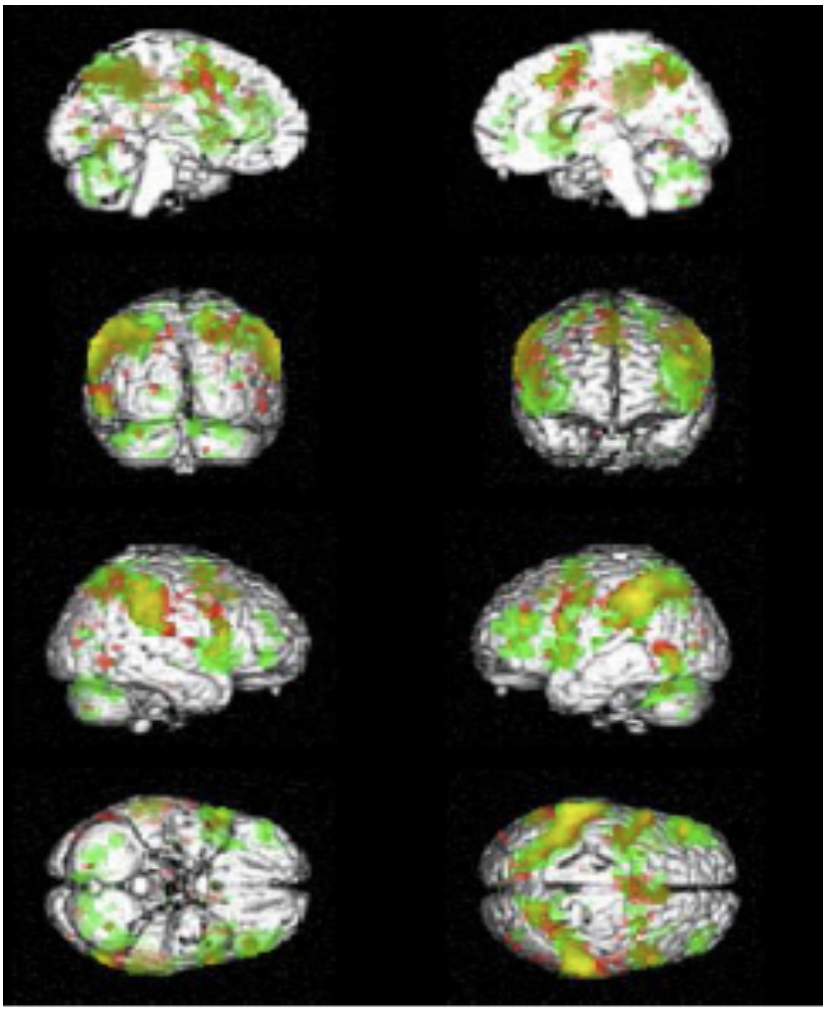

Figure 8.7 Combined activation for LSR (green) and HSR (red) group negatively correlated with activation in the ventromedial seed region. Yellow regions indicate combined areas of activation

When comparing images combining the positively (red) and negatively (green) correlated activity with the vmPFC seed (Figure 8.8), it is seen that the LSR looks similar to the whole group in the extent of areas correlated with the seed region. On the other hand the HSR group shows less extensive patterns of connectivity comparison to the whole group. More limited areas of activation were seen in the anterior part of the frontal lobes, posterior/parietal and temporal regions. Limited deactivation was seen in the posterior cerebellum. On the right and left sides of the cortex, there was limited activation in frontal and parietal areas and less extensive deactivation in sensory/motor areas. On the superior part of the cortex, there were less extensive areas of activation in frontal and parietal regions. There was a lack of deactivation seen in the cerebellum and more limited activation in frontal and posterior regions on the inferior surface.

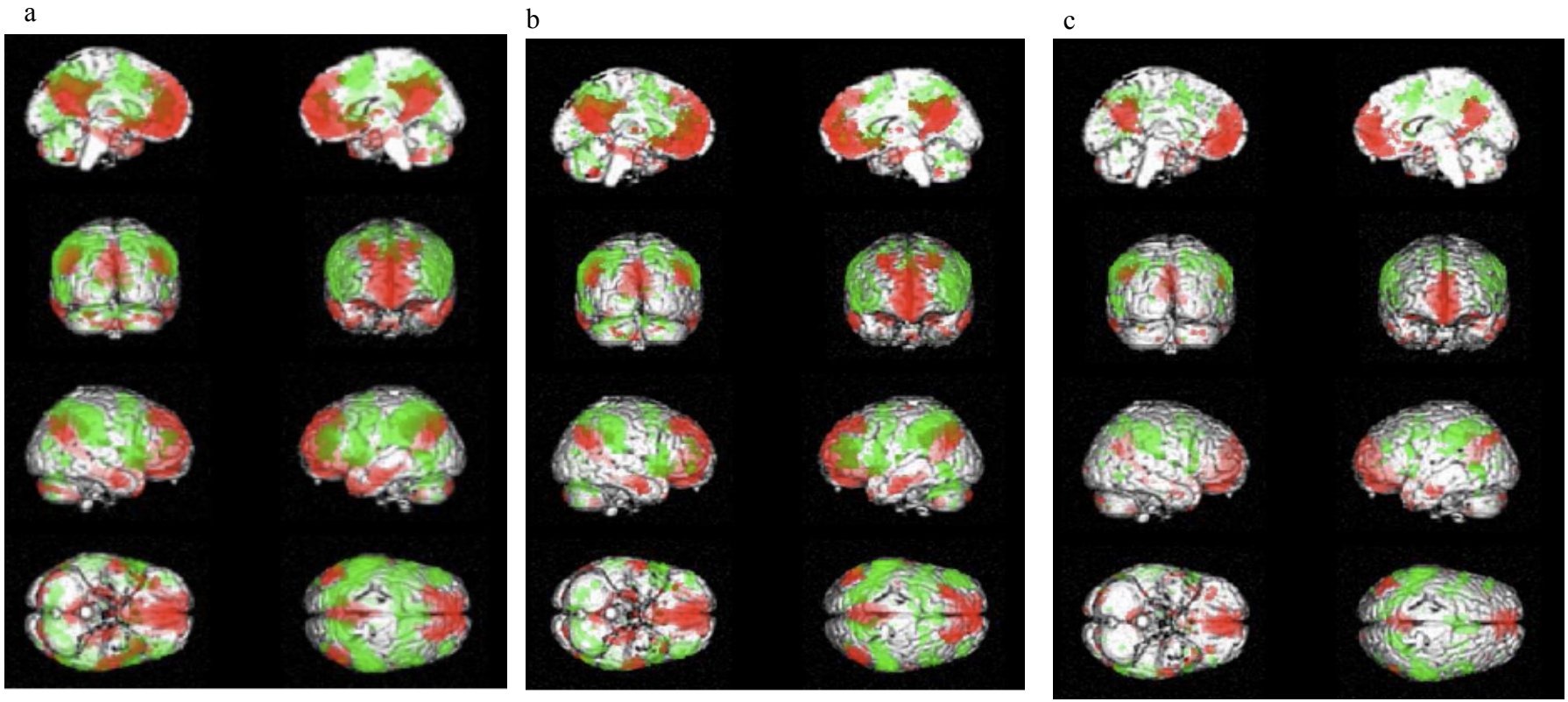

Figure 8.8 Activations associated with positive (red) and negative (green) correlation with activity in ventromedial seed for the whole group (a) LSR group (b) and HSR group (c). The left side of the brain is on the left side of each image. From left to right and top to bottom the 8 images in each panel are left medial, right medial, posterior, anterior, left lateral, right lateral, inferior, and superior

8.6.4. Inspection Time

Behavioural Results

Of the 30 participants who took part in the fMRI scanning, not all were included in the analysis of the inspection time test. The threshold of inclusion for the data of a particular participant was above a threshold of 90% correct (31.5/35) for highest duration (97ms) and above chance (17.5/35) on the shortest exposure. Four participants from both the LSR group and the HSR group were excluded from the 2nd level analysis leaving 11 participants in both the LSR group and HSR groups.

Inspection Time performance was compared across levels of the task and between the HSR and LSR groups. Behavioural results were analyzed to determine any systematic differences between groups. Results of repeated measures ANOVA showed that there was a significant difference in accuracy with increasing accuracy as the length of stimulus exposure increased $F(1.64, 34.52) = 36.2$, $p<.001$ (Greenhouse-Geisser corrected *df* used due to violation of assumption of sphericity). Contrasts between each increasing level of stimulus exposure were significantly different, 31ms > 15ms, $F(1,21)=13.05$, $p<.01$, $r=.62$; 47ms>31ms, $F(1,21)=30.70$, $p<.001$, $r=.77$; 81ms>47ms, $F(1,21)=15.21$,$p<.01$, $r=.65$. This was true for all except the last 2 given near perfect responses in both the 81 and 97 ms exposure, $F(1,21)=.148$, $p=.70$, $r=.08$, as shown in *Figure 8.9*. In line with Waiter and colleagues (2009), easy trials were defined as those at

ceiling (32/35) including 47, 81, and 97 ms and hard trials were defined as those above chance (17.5/35) and below ceiling (32/35) including 15 and 31. Note on 31 ms the LSR group achieved a mean of 31.55 – at 90% - possibly 15 ms the only "hard" level for comparisons.

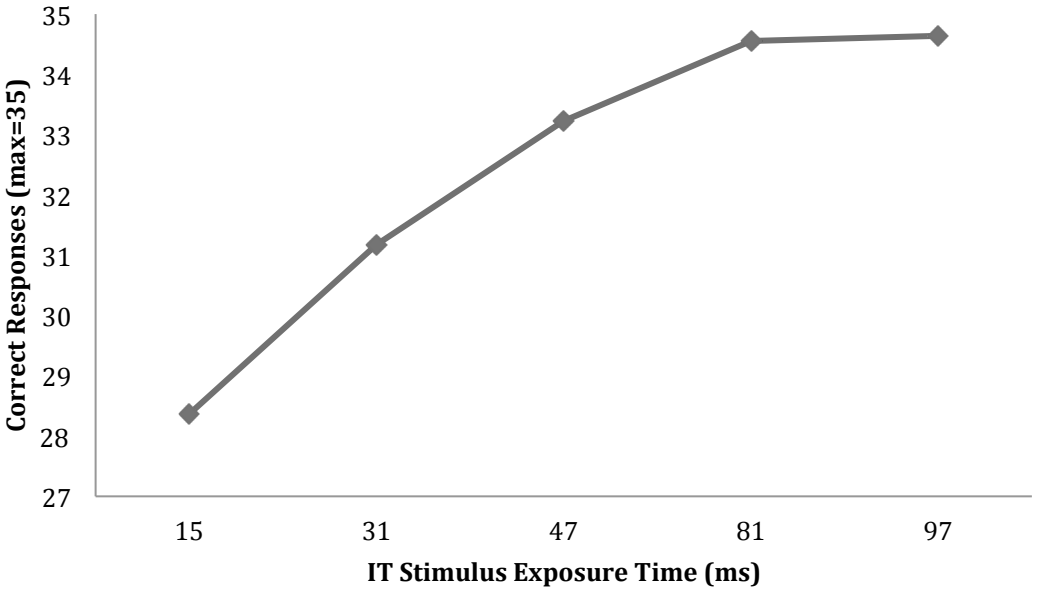

Figure 8.9 Change in Accuracy with Increasing Stimulus Exposure on the Inspection Time Test

Overall, participant response time decreased with increasing stimulus exposure time, F(2.06, 43.24)=29.79,p<.001 (Greenhouse-Geisser corrected *df* used due to violation of assumption of sphericity) shown in *Figure 8.10*. Contrasts between increasing level of stimulus exposure were significantly different, 31ms > 15ms, F(1,21)=18.05, p<.001, r=.68; 81ms>47ms, F(1,21)=12.68,p<.01, r=0.61 with a trend in this direction for 47ms>31ms, F(1,21)=4.30, p=.051, r=0.41. At the 2 longest exposure levels, response time was equivalent, F(1,21)=.311, p=.58, r=.12.

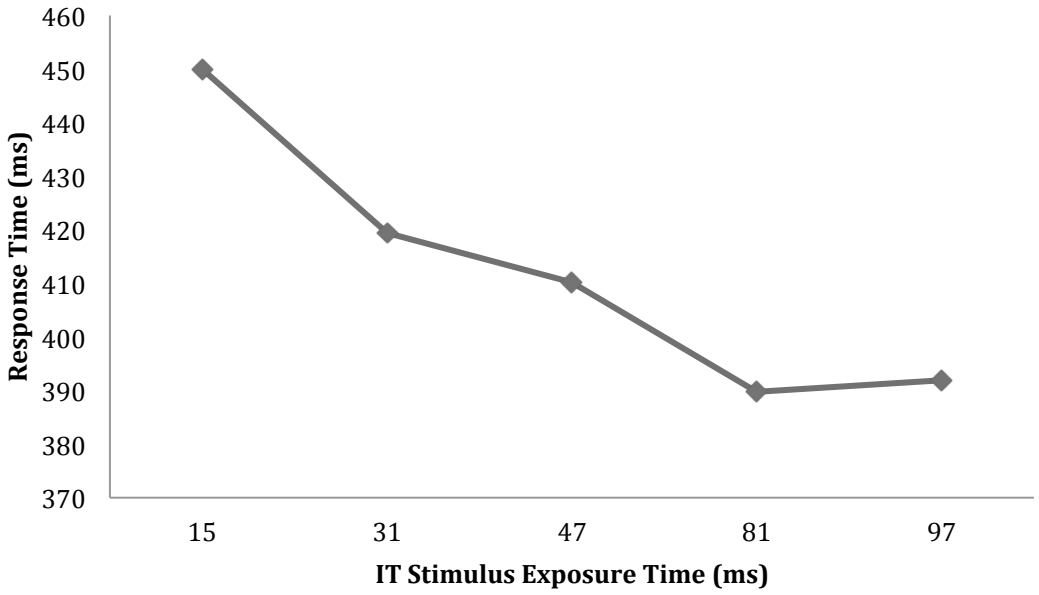

Figure 8.10 Change in Response Time with Increasing Stimulus Exposure for the Inspection Time Test

The LSR and HSR groups were compared on performance at each level of the inspection time test. Results are displayed in Table 8.20. Although the HSR group consistently displayed a numerically higher response time than the LSR group, this time was not statistically different. Results of t-test indicated there was no difference in the accuracy of responses between the LSR and HSR group at any stimulus duration.

Table 8.20 *Comparison of Retinopathy Group on Inspection Time Accuracy and Response Time at each Stimulus Duration*

IT Stimulus Duration (ms)	**Measure**	**LSR (n=11) Mean (SD)**	**HSR (n=11) Mean (SD)**	***t (20)***	***p***
15	# Correct	29.36 (4.4)	27.36 (4.6)	1.04	.32
	RT *ms*	426.97 (90.1)	473.09 (88.1)	-1.21	.28
31	# Correct	31.55 (2.3)	30.82 (2.3)	.747	.46
	RT *ms*	393.75 (67.2)	444.97 (67.6)	-1.78	.09
47	# Correct	33.27 (1.8)	33.18 (2.3)	.102	.92
	RT *ms*	388.64 (71.0)	431.82 (76.1)	-1.38	.28
81	# Correct	34.73 (.65)	34.36 (1.0)	.994	.34
	RT *ms*	375.85 (56.9)	403.65 (60.9)	-1.11	.28
97	# Correct	34.73 (.47)	34.55 (1.0)	.531	.60
	RT *ms*	377.3 (71.2)	406.62 (57.0)	-1.07	.30

IT=Inspection Time; RT=Response Time in ms
*$p<.05$, 2-tailed

fMRI Group Results Inspection Time

Whole group results were examined to determine the areas of negative and positive correlation with task difficulty. Cluster maxima greater than a voxel extent of 10 and threshold of $p<.005$, uncorrected were identified. Those areas of activation with a negative correlation to stimulus duration (increasing difficulty) included primarily small

areas in the frontal regions (medial frontal gyrus, superior frontal gyrus, and cingulate cortex (Table 8.21) shown in Figure 8.11.

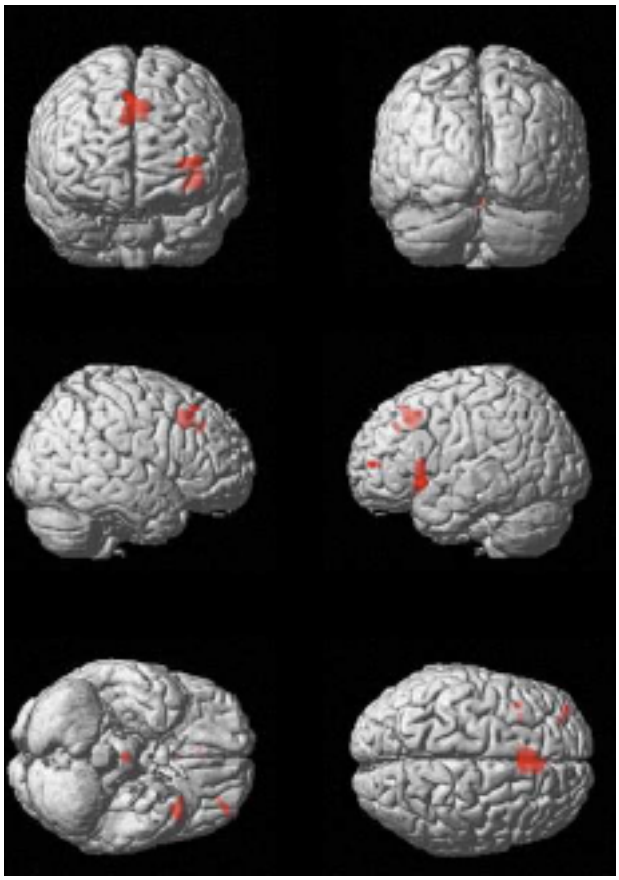

Figure 8.11 Activation on Inspection Time task negatively correlated with increasing duration (increasing task difficulty) whole group

Table 8.21 *Regions with negative correlation to stimulus duration (increasing task difficulty) on inspection time for whole group*

Region	Lat	BA	MNI (x,y,z)			Vox.	Z score
			x	y	z		
Frontal							
Inferior Frontal Gyrus	L	47	-40	18	-6	109	4.40
Inferior Frontal Gyrus	L	47	-32	20	-10		3.05
Superior Frontal Gyrus	R	8	6	30	50		3.15
Superior Frontal Gyrus	L	-	-30	48	6		2.88
Middle Frontal Gyrus	L	10	-38	54	8	19	3.22
Medial Frontal Gyrus	R	9	2	36	36	20	2.77
Limbic							
Insula	L	13	-40	16	8		3.20
Cingulate Gyrus	L	32	-4	24	42	226	3.63
Cingulate Gyrus	R	32	8	22	36		3.32
Claustrum	L	-	-32	18	4	12	2.90
Brainstem							
Red Nucleus	L	-	0	-20	-20	23	3.59

MNI coordinates (x,y,z) refer to peak voxels within cluster maximum reported $p<.005$, 10 voxel extent. MNI space. Lat.= laterality; BA= approximate Brodmann's location; Vox. = number of significant voxels;

There were several large areas indicating a positive correlation in BOLD activation with increasing stimulus duration (decreased difficulty), primarily in posterior regions (superior temporal gyrus, middle occipital gyrus, precuneus, posterior cingulate) and some frontal areas (superior and middle frontal gyrus). These areas are listed in Table 8.22 and shown in Figure 8.12

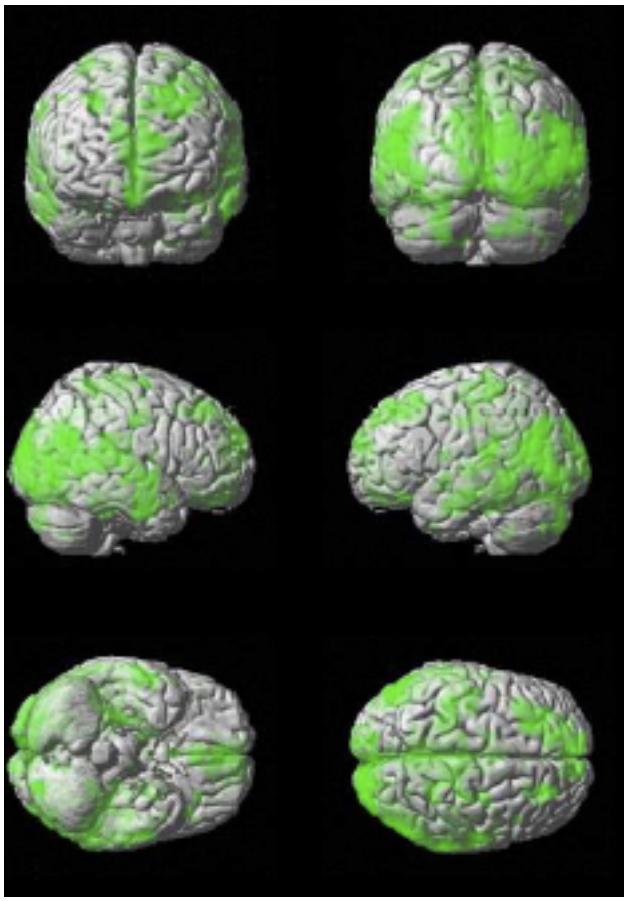

Figure 8.12 Activation on Inspection Time task positively correlated with increasing duration (decreasing task difficulty) whole group

Table 8.22 *Regions with negative correlation to stimulus duration (increasing task difficulty) on inspection time for whole group*

Region	Lat	BA	MNI (x,y,z)			Vox.	Z score
			x	y	z		
Frontal							
Inferior Frontal Gyrus	L	47	-42	24	-20	39	3.21
	L	47	-30	32	-20	28	3.02
	R	46	44	38	8	12	2.83
Medial Frontal Gyrus	L	10	-12	58	20	2107	4.61
	L	9	-14	42	36	20	3.16
Middle Frontal Gyrus	R	8	24	36	46	316	4.56
	L	8	-26	30	42	1087	4.31
	R	6	28	-10	56	31	3.80
	L	6	-18	-12	64	14	3.54
	R	8	48	16	46	23	3.06
Superior Frontal Gyrus	L	6	-16	-6	74	26	3.15
Paracentral Lobule	L	5	-24	-44	48	29	3.44
Precentral Gyrus	L	6	-60	0	10	38	3.92
	R	4	58	-16	36	136	3.64
	L	6	-42	-20	64	57	3.27
	R	4	24	-24	54	13	3.01
	L	6	-60	-12	40	25	2.92
Temporal							
Fusiform Gyrus	L	20	-46	-2	-26	20	3.31
	R	20	40	-22	-28	14	3.18
Inferior Temporal Gyrus	R	20	44	-14	-34	16	3.57
Middle Temporal Gyrus	L	21	-44	8	-38	14	3.23
	R	39	32	-60	26	21	2.94
Superior Temporal Gyrus	R	38	56	12	-20	19	3.50
Superior Temporal Gyrus	L	22	-44	-24	-8	16	3.06

Table 8.22 (cont.)

Region	Lat	BA	MNI (x,y,z)			Vox.	Z score
			x	y	z		
Parietal							
Postcentral Gyrus	R	3	40	-28	58	25	3.01
Precuneus	L	31	-12	-54	28	24171	5.76
Superior Parietal Lobule	L	7	-22	-60	66	14	3.26
Limbic							
Amygdala	L	-	-30	-4	-28	169	4.16
Anterior Cingulate	R	32	14	46	-10	15	3.62
	L	24	0	20	16	50	3.25
Sub-Lobar							
Caudate	L	-	-18	-6	22	24	3.21
	L	-	-10	4	16	11	2.81
Insula	R	13	38	2	18	27	3.74
	L	13	-34	-28	20	47	3.30
	R	13	38	-10	18	11	3.26
	L	13	-44	-10	8	14	3.01
Lentiform Nucleus	L	-	'	-18	-6	143	4.19
	L	-	-20	6	8	110	3.59
	L	-	-22	-10	2	17	3.40
Thalamus	L	-	-20	-26	6	23	3.31
	L	-	-8	-14	2	22	3.24
Cerebellum							
Cerebellar Tonsil	L	-	-28	-44	-50	52	3.67
	L	-	-48	-48	-42	16	3.18
	R	-	28	-54	-42	10	3.12
Inferior Semi-Lunar Lobule	L	-	-8	-72	-48	35	3.31

Table 8.22 (cont.)

Region	Lat	BA	MNI (x,y,z)			Vox.	Z score
			x	y	z		
Pyramis	L	-	-44	-72	-42	40	3.34
	R	-	46	-68	-44	16	2.97
Culmen	R	-	14	-48	-16	20	3.18

Listed regions are SPM clusters containing at least 10 significant voxels (p <005, uncorrected. MNI coordinates (x,y,z) refer to cluster maxima reported in MNI space. Lat.= laterality; BA= approximate Brodmann's location; Vox. = number of significant voxels; Inf=inferior

When comparing activation for the LSR and HSR group related to task difficulty there was greater activation for the LSR group when stimulus duration increased (decreasing task difficulty) in several areas. Cluster maxima are reported in Table 8.23 and shown in Figure 8.13.

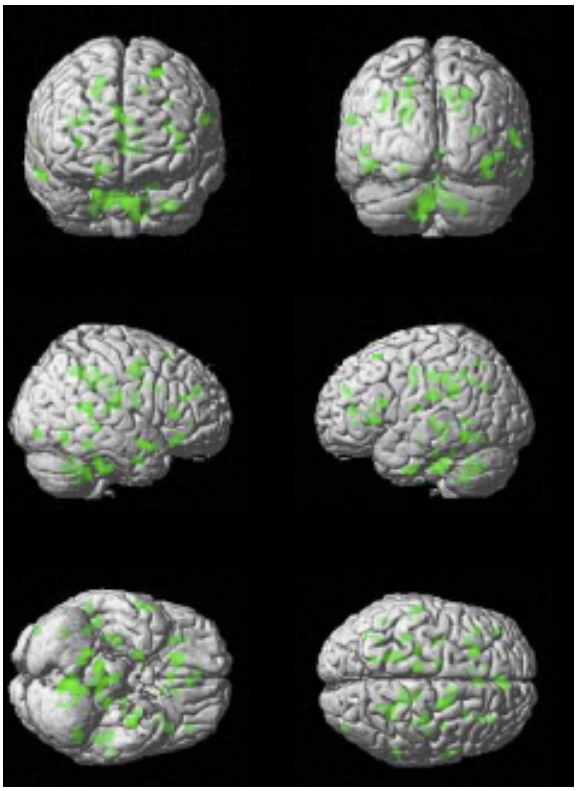

Figure 8.13 Activation on Inspection Time task positively correlated with increasing duration (decreasing task difficulty) LSR group >HSR group

Table 8.23 *Regions with positive correlation to stimulus duration (decreasing task difficulty) on inspection time for LSR group>HSR group*

Region	Lat	BA	MNI (x,y,z)			Vox.	Z score
			x	y	z		
Frontal							
Inferior Frontal Gyrus	L	47	-40	24	2	21	3.44
	R	47	32	30	8	24	3.30
Medial Frontal Gyrus	R	25	12	30	-14	59	3.69
	R	9	4	46	26	36	3.49
Middle Frontal Gyrus	L	10	-40	40	12	12	2.94
	R	10	30	36	20	13	2.87
Superior Frontal Gyrus	L	8	-24	22	56	28	3.44
Occipital							
Inferior Occipital Gyrus	R	18	40	-86	-8	14	2.92
Fusiform Gyrus	R	37	40	-44	-18	21	3.74
	R	37	38	-62	-14	31	3.42
Temporal							
Inferior Temporal Gyrus	L	20	-36	-6	-40	42	3.81
Middle Temporal Gyrus	R	21	60	2	-18	28	3.58
	L	21	-48	-50	2	11	3.33
Sub-Gyral	L	37	-44	-52	-10	41	3.94
Superior Temporal Gyrus	R	41	44	-36	-2	29	3.50
	L	-	-46	-24	2	42	3.31
	R	22	58	-42	12	27	3.25
Parietal							
Inferior Parietal Lobule	L	40	-34	-34	36	32	3.57
	L	40	-34	-56	34	18	2.85
Postcentral Gyrus	L	40	-60	-22	22	31	3.31

Table 8.23 (cont.)

Region	Lat	BA	MNI (x,y,z)			Vox.	Z score
			x	y	z		
Precuneus	L	7	-18	-50	40	27	4.07
	R	7	26	-48	42	61	3.89
	L	7	-14	-58	50	16	2.82
Limbic							
Anterior Cingulate	R	24	2	26	12	42	3.86
	L	24	-10	30	4	16	3.36
	L	32	-4	40	0	12	3.14
Cingulate Gyrus	L	31	-20	-44	28	110	4.52
	R	24	18	-2	48	107	4.11
	R	31	12	-36	40	124	3.94
	R	24	8	4	32	21	3.67
	L	31	-10	-26	40	49	3.65
	L	31	-24	-26	40	20	3.34
	L	24	-14	-6	40	21	3.07
Parahippocampal Gyrus	L	19	-22	-58	-12	21	3.40
	L	28	-20	-14	-14	10	3.02
Uncus	R	28	18	-2	-30	28	3.58
Sub-Lobar							
Caudate	L	-	-8	18	18	13	3.43
Claustrum	R	-	32	-18	20	113	4.10
Insula	L	13	-32	16	18	24	3.46
	R	13	38	-4	20	22	3.19
Lentiform Nucleus	L	-	-24	-14	10	13	2.80
Cerebellum							
Culmen	R	-	10	-34	-34	186	3.81
	R	-	4	-32	-20	15	3.49

Table 8.23 (cont.)

Region	Lat	BA	MNI (x,y,z)			Vox.	Z score
	L	-	-18	-26	-24	19	3.26
	R	-	4	-58	-2	13	2.96
Nodule	L	-	-8	-64	-34	205	3.74
Cerebellar Tonsil	R	-	22	-44	-42	65	3.66

Listed regions are SPM clusters containing at least 10 significant voxels (p <005, uncorrected. MNI coordinates (x,y,z) refer to cluster maxima reported in MNI space. Lat.= laterality; BA= approximate Brodmann's location; Vox. = number of significant voxels; Inf=inferior

The LSR group showed higher activation with decreasing stimulus duration (increasing difficulty) in only one area in the cerebellum, the right culmen (x=12,y=-32,z=-12).

8.7. Discussion

8.7.1. N-Back

Functional MRI results for the whole group indicated several areas of activation with increasing task difficulty on the n-back task. The group shows similar areas of activation with increasing task difficulty on a multi-scanner evaluation of the n-back using a similar block design (Gradin et al. 2010). Between group results indicate that the group with high severity of retinopathy showed greater activity than the group with low severity of retinopathy in several frontal areas and less deactivations in areas included in the default mode network. These regions are part of those identified through resting state analysis

to be part of the anterior default mode network (DMN) by Damoiseaux and colleagues (2008) including the superior and middle frontal gyri (BA 11) and near the areas involved in task-induced deactivations in the Persson and colleagues (2007) study including the left precuneus BA 31 (11 -52 49), and right medial frontal BA 9 (11 49 21). In general this is consistent with the finding of absent or less deactivation in DMN of older groups in comparison to younger groups.

The combination of retinopathy and age indicated that younger people with high severity of retinopathy show activations in comparison to deactivations across a number of areas in relation to the older group with low severity of retinopathy, supporting the hypothesis of accelerated ageing. The fact that there were no areas of greater activity for the older adults with low severity of retinopathy over the younger adults with high severity of retinopathy also supports the idea that the retinopathy places an added burden to BOLD function over age.

8.7.2. Functional Connectivity: Resting State fMRI

Resting state fMRI methods were used to explore the possible differences in functional connectivity between the low severity and high severity retinopathy groups and how these differences compare to the results found in ageing research. A seed region was identified through research on the hippocampal cortical memory system, part of the default mode network (Vincent et al., 2008).

Results for the whole group indicated both anterior and posterior regions active in resting state that included those identified by

Damoiseaux and colleagues (2008) in their study of functional connectivity in ageing. Investigation of the positive and negative correlations to activation in the vmPFC seed ROI indicated that, consistent with evidence in ageing research, the group with high severity retinopathy showed lower connectivity (less extensive connections, scattered smaller regions of activation) than the group with lower severity retinopathy or the group as a whole. They also showed a lack of correlations in the cerebellum which also contributes in the DMN (Habas et al., 2009). This is consistent with the evidence of less functional connectivity and less overall activity in resting state (Reuter-Lorenz, & Park, 2010) in normal cognitive ageing and the findings from Damoiseaux and colleagues (2008) of lower BOLD activity in older compared to younger subjects in the anterior and posterior resting state networks. A recent study of resting state in older adults with T1DM also came to the conclusion of decreased connectivity in resting state networks for individuals with proliferative retinopathy in comparison to controls (Van Duinkerken et al., 2011).

8.7.3. Inspection Time

Although in similar regions, the activation positively correlated with task difficulty was not as extensive in frontal regions for the study group in comparison to the research by Waiter and colleagues (2008). There was also more extensive activation in posterior regions. In the Waiter and colleagues (2008) study, they compared results of sustainers, those who had maintained cognitive function as measured at age 11, and decliners, those who showed a decline in cognitive

function since age 11, and results from a younger age group. Although not as extensive as in the Waiter and colleagues (2008) study, the low severity retinopathy group, like the sustainers, showed a positive correlation in activation with increasing stimulus duration (decreasing task difficulty). In the Waiter and colleagues (2008) study, the decliners showed an absence of positively correlated activity with decreasing task difficulty. There were no areas in which the high severity retinopathy group, like the decliners, showed greater activation over the low severity retinopathy group with decreasing task difficulty. The group with higher severity retinopathy showed a similar pattern to the decliner group and the low severity retinopathy a similar pattern to the sustainer group. This is in line with the hypothesis that the high severity retinopathy accelerates decline in brain function.

8.7.4. Conclusions

What do the results tell us about cognitive ageing in T1DM and its relationship with theories of cognitive ageing?

In the Scaffolding Theory of Ageing and Cognition (STAC), Park and Reuter-Lorenz (2009) argue that increased prefrontal recruitment and low levels of default mode network engagement should be considered protective of cognitive function in ageing and increases the ability of the ageing brain to use complementary, and alternative neural circuits to achieve a cognitive goal. These researchers view this as "self-generated support of cognitive function" (Park & Reuter-Lorenz, 2009, p. 175). Indeed, in the current study

there was no difference between the cognitive performance of those with high and low severity retinopathy on either the inspection time or the n-back tasks completed in the fMRI. They suggest that middle-aged adults who show scaffolding that is like that of older adults may be at risk for poorer cognitive outcomes and age-related deficits and is a response to underlying vulnerability that may be sub-clinical. In the study group, although matched in age, those with high severity of retinopathy appear to be more like older adults in their pattern of task activations/deactivations and functional connectivity. These results provide evidence of accelerated ageing in this group.

Chapter 9
General Discussion

9.1. Conclusions

The aim of this thesis was to evaluate the evidence of accelerated cognitive and brain ageing within a middle-aged to older adult group with T1DM and to identify modifiable protective factors of cognitive function. As such, diabetes health, general health, psychological factors and their relation to outcomes on cognitive processing tests were the focus of the cognitive study and investigation of MCI and psychological variables in the study group. The combined results of these studies led to the focus on microvascular disease, specifically retinopathy, in the neuroimaging investigation in the search for evidence of functional brain ageing in the group with higher severity of retinopathy. The common thread through these studies is maintaining a view on the normal cognitive and brain ageing process to understand how this chronic disease impacts both cognitive and brain function in ageing.

Although the research into cognition in T1DM has emphasized the mild to moderate impact of this chronic disease on only specific aspects of cognitive function (Brands et al, 2005; Brands et al., 2006, Ryan, 2005), these conclusions have been primarily based on the results of cognitive testing and structural imaging and without the consideration of the normal ageing process. The cognitive reserve theory suggests that cognitive function is maintained through neural compensation, or the use of alternative brain networks (Stern, 2009).

The STAC model (Park & Reuter-Lorenz, 2009) suggests that the brain uses functional scaffolding to re-allocate and re-distribute neural resources with the aim to maintain cognitive function, and compensate for structural brain changes in ageing. The STAC model emphasizes that functional changes are evident before cognitive ones and early scaffolding processes may be initiated when there is disease that affects brain structure. Functional brain changes then can minimize cognitive changes and compensate for structural changes. Ultimately, investigation of brain function is necessary to confirm evidence of accelerated ageing in adults with T1DM. This methodology has only been used in a limited way in previous T1DM research (Van Duinkerken et al., 2011; Wessels et al., 2006).

The research involved four components. First, cognitive testing was used to identify the strongest diabetes health predictor of cognitive function and to determine whether the group showed evidence of cognitive deficits below the norm for age. Mild deficits, within the normal range, were confirmed for those with higher severity of microvascular disease, specifically retinopathy. Second, results of the cognitive study were extended to focus on the group who met criteria for MCI, confirming that retinopathy is the strongest diabetes health predictor of MCI group membership. Third, psychological factors, both general and diabetes-specific, were explored in relation to diabetes health variables and potential influence on cognitive function to determine modifiable factors that show a relationship with cognitive function in this older adult group. Finally, a functional MRI

(fMRI) paradigm, including both cognitive tasks and resting state functional connectivity methods, was used to determine whether groups who differed on severity of retinopathy would show functional brain differences. This finding would support the presence of early scaffolding and therefore an accelerated ageing process. The conclusion supported through these studies is that the microvascular damage present in those with severe retinopathy engages an early scaffolding process that would serve to preserve cognitive function and limit cognitive impairment through the same process seen in normal ageing. Optimal management of diabetes and the prevention or minimization of microvascular disease, engaging in scaffolding enhancing activities (cognitive engagement, exercise) and attention to psychological well-being can enhance this scaffolding process leading to better cognitive outcomes.

Together, results of the cognitive and neuroimaging studies highlight the importance of severity of microvascular disease in the prediction of cognitive function and brain function for middle aged and older adults with T1DM above other measures of diabetes health. There was some evidence that estimated cognitive decline and MCI were related to a higher frequency of hypoglycaemic events and that groups with low HbA1c levels had the weakest cognitive outcomes on some measures. This suggests there may be greater vulnerability of an older adult group to tight glycaemic control and related increase in risk of hypoglycaemia that has not previously been identified based on the studies of younger adult groups with T1DM. Having severe

retinopathy also appeared to lead to vulnerability to the extremes of long-term glycaemic control. Results suggest that once microvascular complications are present, long-term glycaemic control on its own is a less important factor in differentiating cognitive function in this group than for younger adults who do not have as high an incidence of this severe microvascular complication. Although tight control is advised to minimize microvascular disease, older adults may be more susceptible to an increased risk of hypoglycaemic events than their younger counterparts. Chronic low glucose may not be devoid of cognitive costs as suggested in studies of relatively younger groups (Jacobson et al., 2007 & 2010). The finding of a higher incidence of MCI and age-related cognitive impairment, in this primarily middle-aged group supports the premise that an early process is occurring. Psychological factors, and specifically feelings related to diabetes, were explored as possible ways to optimize outcomes in ageing and the group showed positive well-being overall. Diabetes well-being was found to have a positive relation with both cognitive function and glycaemic control and anxiety a negative relation with microvascular complications. Harnessing the positive attitudes present generally in older adults with T1DM, working to maintain positive attitudes regarding diabetes, and finding a "functional" level of worry can facilitate self-management, and support the control of microvascular disease that would support optimal cognitive outcomes. Finally, the results of fMRI confirm that there is early scaffolding apparent in groups with more severe retinopathy through the functional results that

show consistent similarities with findings in normal ageing. When compared to the group with low severity of retinopathy, results indicated an increase of frontal activity and limited deactivation of areas related to the default mode network (DMN) on the working memory task. A pattern similar to cognitive "decliners" (Waiter et al., 2008) was seen on the inspection time task and limited functional connectivity was seen in resting state.

The combination of neuropsychological testing and neuroimaging in this study highlight that mild differences in cognitive function in comparison to age norms are maintained by changes in brain function that keep pace with and provide effective scaffolding for the earlier cognitive ageing process in this group with consequences that are generally not debilitating. Although deficits are mild, Wrighten, Piroli, Grillo, and Reagan (2009) suggest that, "the potential unfortunate outcome of these 'mild' cognitive deficits in T1D patients is a predisposition for more rapid deterioration of cognitive function in later life" (p.445) and the structural brain changes that underlie these cognitive changes are likely to have negative consequences for functioning over time.

These results highlight the potential areas for intervention and recommendations for preservation of cognitive function in this group. This includes maintaining glucose control to limit the onset and severity of microvascular disease and maintaining cognitive activity and engaging in exercise. Activities that promote positive emotional health and a functional level of worry about self-management will help

middle aged and older adults make or maintain these health habits that relate to better cognitive outcomes.

9.2. Limitations and Critique

The fact that no control group was used in this study may be considered a limitation in methodology as the determination of cognitive deficits was not based on a matched cohort and brain functioning could not be compared on the same measures under the same parameters. However, this was an intentional choice to focus on the potential important diabetes health variables that may particularly affect cognitive function. As a method of comparison, cognitive results were translated to standardized z scores and evaluated in relation to results of the normative age group. Comparison was made to results of population studies, and care was taken to equate methodology as much as possible in the fMRI study. Another criticism is that with 94 participants in the cognitive study there were a limited number of variables that could be included in multiple regression analysis. In contrast, the DCCT/EDIC study (Jacobson et al., 2011) had over 1000 participants, increasing the power to find relationships among variables. To overcome this limitation, care was taken to choose fewer predictors to include in regression analyses. In comparison, other studies of older adults in T1DM have used a small sample size ($n \leq 40$) and this is a relatively large group. Three studies have followed the same sample (Van Duinkerken et al., 2011; Brands et al., 2006, Brands et al., 2007) comparing this group over time, or to control groups and groups with T2DM. Another study compared cognitive functioning of

45 to 64 year olds (n=39) to controls of the same age and younger groups with T1DM 18 to 44 (Ryan, 2005). The large DCCT/EDIC study has thus far focused mainly on a relatively younger age group (Jacobson et al., 2007).

The cross-sectional design with correlation-based statistics, does not allow for cause and effect inferences. The results lead to a discussion of relationships between variables, however the direction of these relationships and possible third variables involved are undetermined. A control for this included controlling for factors that might have a relationship with variables of interest.

As well, the measure of microvascular disease was a combination of retinopathy, neuropathy, and nephropathy due to low numbers with high severity of the two latter diseases. It was therefore not possible to determine if one type of microvascular disease had a greater influence than another on cognitive function. In most cases the combined score of microvascular disease did have stronger correlational values to cognitive function than retinopathy on its own, suggesting that the addition of neuropathy and nephropathy ratings increased the predictive value over retinopathy alone.

Although the neuropsychological tests used in this study are the ones commonly used in other studies of individuals with T1DM, these tests notoriously are not pure measures of the cognitive processes they purport to measure. Although the cognitive processes identified in this study are those identified in research of these measures, other cognitive processes may also play a part in cognitive performance on

these tests, or may be primarily responsible (e.g. graphomotor speed on a processing speed task), limiting the assurance that a certain cognitive process is responsible. The cognitive tests used for neuroimaging are more pure measures of the cognitive processes they measure and are related to common areas of BOLD activation and deactivation. The addition of fMRI techniques moves the focus from the cognitive process to the brain function supporting the cognitive process.

9.3. Future Directions

The relationships between diabetes variables, cognitive function, and brain function highlighted in this thesis suggest possible areas that need to be explored to better understand cognitive and brain ageing in T1DM. In future, a prospective study of older adults would follow a group across time to track actual changes in cognition and effects over time. This would also allow follow-up with those who met criteria for MCI to determine outcomes for this group and rate of progression to dementia.

Experimental studies would allow the ability to determine cause and effect relationships on cognitive function and MCI for interventions including controlling blood glucose, cognitive activity, exercise, and methods to promote well-being. They would lead to confirmation of these relationships and more specific recommendations on ways to promote healthy cognitive ageing in this group. Creating a diabetes-specific age-normed measure to accurately identify anxiety and diabetes within the T1DM population and operationalizing the

functional level of anxiety suggested by the results of the current study, could contribute to tailoring patient guidance to improve self-management. Future fMRI studies could focus on direct comparison of younger and older groups with and without retinopathy to more specifically identify differences related to ageing and the added impact of retinopathy.

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Appendices

Appendix A

Cognitive Study: Consultant Patient Invitation Letter

Dear

With colleagues from the University of St. Andrews we are running a research study in the NHS Tayside Diabetes Centres looking to see if there is any effect of blood glucose level control on the way in which people with Type 1 diabetes think and reason.

We wonder whether you might be willing to help with this research, which involves an interview, including some problem-solving tasks and a questionnaire about how you are feeling. I am enclosing a copy of the information sheets which provide some more information.

Please try and read through this information sheet thoroughly prior to deciding whether you would like to take part in this study. It is entirely your choice whether or not you do so and you do not need to give any reason for not participating. Please also note that such a decision will not affect your treatment in any way.

If you are interested in helping with this research project, or if you would definitely not want to discuss it when you attend the clinic, I would be grateful if you could contact Harriet Johnston, research psychologist, by phone or by posting the attached response card (stamp included). Her contact details are provided on the information sheet.

If you would like to obtain further information or talk about this study please do not hesitate to telephone the number provided so that Harriet can get back to you. Many thanks for giving this your attention.

Yours sincerely,

Dr. Rory McCrimmon

Honorary Consultant Diabetologist, Strathmore Diabetes Centre

Appendix B

Cognitive Study: Introductory Letter

University of St Andrews

School of Psychology

Tel: +44 01382 496483
Email: hjohnston1@nhs.net

_____, 2010

Dear

Title: Thinking and Reasoning in Type 1 diabetes

We are currently carrying out a research project at the _____ Diabetes Centre and are writing to ask if you would like to take part.

In the project we are investigating the impact of blood glucose level control on a variety of areas of thinking for people with Type 1 diabetes.

The enclosed Participant Information Sheet gives you more information about the project and what you have to do if you decide to take part. Before you decide you might want to discuss this with your spouse or other members of your family. You can also discuss it with the staff at the diabetes centre or contact me, Harriet Johnston, on 01382 496483 if you have any questions.

If you would like to take part, please contact me or complete and return the enclosed response card. **If you do not wish to take part then you do not have to do anything.**

Once you return the response card and you have indicated that you are interested in the study, you will be contacted by the researcher. A time will be arranged to meet before or after your regularly scheduled appointment at the diabetes clinic or at another time at your convenience. At this meeting the project will be explained to you. After hearing more about the project you decide whether or not to continue. If you wish to participate you will be asked to sign a consent form and complete a number of puzzle-like tasks and questionnaires.

If you decide to participate you can change your mind at any time in the future. Thank you for taking the time to read this letter and information.

Yours Sincerely,

, Researcher, University of St. Andrews

Supervisors:
Dr. Arlene Astell, CClinPsychol, Senior Lecturer, University of St. Andrews
Dr. Rory McCrimmon, Honorary Consultant Diabetologist & Senior Lecturer in Translational Medicine, Strathmore Diabetes Centre/NHS Tayside

February 23, 2010
v2

Appendix C

Cognitive Study: Participant Information Sheet

Participant Information Sheet
Thinking and Reasoning in Type 1 diabetes

You are invited to participate in a research project. This research is part of an educational qualification. The following information is to help you decide if you want to take part. Read it carefully and discuss it with other people if you want. You can ask me any questions and I will do my best to answer them. Take time to decide whether or not you wish to take part.

What is the purpose of the study?
While much is known about the importance of blood glucose level control in diabetes for the maintenance of physical well being, recent evidence indicates that it may also be important in maintaining thinking and reasoning skills. The aim of this project is to find out whether blood glucose control levels may have a subtle impact on thinking and reasoning processes for individuals with diabetes.

Why have I been chosen?
We believe this is a suitable study for you. This project is for people with Type 1 diabetes aged 45 and over who have had diabetes for 10 or more years.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the care you receive or affect your relationship with medical staff looking after you, now or in the future

What will happen if I decide to take part?
If you decide to take part you will complete a short battery of problem-solving, and puzzle-like tasks with the researcher, Harriet Johnston. These *cognitive tasks* should take no more than 45 minutes altogether. You will also be asked to answer a few short questionnaires about how you are feeling, and interview questions about your diabetes, age and health history which should take no more than 15 minutes. As you require an adequate glucose supply to perform your best on the cognitive tasks, before the assessment you will be asked to take a blood glucose measurement (using your personal monitor) to ensure that you are not experiencing hypoglycaemia. If you are below 4 mmol/litre glucose will be provided and a second glucose reading will be required to ensure you are able to begin the cognitive tasks. A current waist and hip measurement will also required as this is not regularly taken at the Diabetes Centre appointment. You can take this measurement at the session or at home. Testing will be completed at the Diabetes Centre that you usually visit. The session will be coordinated with your usual appointment or scheduled at your convenience.

During the interview we will ask to video-record your responses (voice and hands/response sheet) whilst you are performing some of the tasks. We will ensure that there will be nothing on these tapes that could identify you in person and that these tapes will be destroyed once they have been analysed.

What are the possible disadvantages and risks of taking part?
We do not anticipate any health risks from taking part in this study. Due to the length of the interview you may find testing to be tiring, but you will be given plenty of opportunity to take breaks. *We do not anticipate any adverse effects from taking part in this study. If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.*

What are the possible benefits of taking part?
There will be no direct benefit to you by taking part, and your individual results will not be revealed to you. However, we will make any future publications of the findings available to you. It is hoped that this research will improve our knowledge relating to Type 1 diabetes and may influence care practices and information provided to people with diabetes in the future.

What if something goes wrong?
If you believe that you have been harmed in any way by taking part in this study, you have the right to pursue a complaint and seek any resulting compensation through the University of St. Andrews who are acting as the research sponsor. Details about this are available from the research team. Also, as a patient of the NHS, you have the right to pursue a complaint through the usual NHS process. To do so, you can submit a written complaint to the Patient Liaison Manager, Complaints Office, Ninewells Hospital (Freephone 0800 0275507). Note that the NHS has no legal liability for non-negligent harm. However, if you are harmed and this is due to someone's negligence, you may have grounds for a legal action against NHS Tayside but you may have to pay your legal costs.

What will happen to the information collected in the study?
All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognized from it. You will be allocated an anonymous ID code during testing which will be used in place of your name on any future publications. Only group results or anonymous individual data will be communicated in Harriet Johnston's PhD thesis, research publications or at professional and public conferences.

Who is organizing and funding the research?
This research is being completed in fulfilment of PhD requirements for the School of Psychology at the University of St. Andrews. The research is supervised by Dr. Arlene Astell, a chartered clinical psychologist and lecturer at the University of St. Andrews, and Dr. Rory McCrimmon, a consultant diabetologist at the Strathmore Diabetes Centre, NHS Tayside in collaboration with the other Diabetes Centres within NHS Tayside.

What happens now?
If you agree to take part you will be asked to complete a consent form. If you decide not to take part, this will have no bearing on your future care or

treatment from the NHS. If you decide to take part we would like permission to inform your GP. However, if you do not agree to us informing your GP you can still take part. The Tayside Committee on Medical Research Ethics, which has responsibility for scrutinizing proposals for medical research on humans, has examined the proposal and has raised no objections from the point of view of medical ethics. It is a requirement that the research records are made available to monitors from NHS Tayside/and the Regulatory Authorities (the latter applicable ONLY in drug trials) whose role is to check that research is properly conducted and the interests of those taking part are adequately protected.

Contact for Further Information

Thank you for reading this information sheet. If you have further have any further questions feel free to contact me. Dr. Ewan Pearson, a consultant physician at Ninewells Hospital who is not involved in this study, is also available to provide an independent opinion about taking part. You can reach him at 01382 740081

If you have understood the contents of this sheet and wish to take part, either contact Harriet Johnston by leaving a message at 01382 496483, by email hjohnston1@nhs.net , or tick the appropriate box on the enclosed response card and return in the envelope provided.

Appendix D

Response Card

School of Psychology, University of St. Andrews
St. Mary's College
South Street, St. Andrews
Fife, Scotland, KY16 9JP

Study: Thinking and reasoning in Type 1 diabetes

Please check appropriate box and return in envelope provided

☐ Yes. I would like to be contacted for more information about this study.

Preferred Contact Telephone Number(s)
_____ / _____

Preferred Contact Time: ☐ AM _____ ☐ PM _____

☐ No. I do not want further contact regarding this study.

ID # _____

Appendix E

Cognitive Study: Inclusion Exclusion Telephone Interview

Inclusion Criteria

How old are you? _____

☐ age over 45

When were you diagnosed with diabetes?

☐ duration 10 or more years _____

Is English your first language? If not, are you comfortable with both speaking and reading in English? _____

☐ English speaker

Exclusion Criteria

Currently or in the past have you had any condition or injury affecting your thinking, reasoning or memory skills such as head injury, coma, stroke, epilepsy, dementia etc.

☐ Injury or disease directly affecting the brain _____

Have you been diagnosed with a mental health or thought disorder for which you require medication (e.g. anxiety, depression, schizophrenia)

☐ Psychiatric disorder _____

Do you drink alcohol? If so how many units per week?

☐ Drug or Alcohol problem/addiction _____

Do you have any difficulties with your hearing or vision? _____ If yes, do you wear glasses/hearing aids that correct for this?

☐ Uncorrected hearing/vision _____

Appendix F

Cognitive Study: NHS Ethics Favourable Opinion

NHS Fife NHS Forth Valley NHS Tayside

Fife, Forth Valley & Tayside Research Ethics Service

Tayside Committee on Medical Research Ethics A
Research Ethics Office
Residency Block
Level 2
Ninewells Hospital & Medical School
DUNDEE
DD1 9SY

Mrs Harriet Johnston
PhD Student
St. Andrews
School of Psychology
St. Mary's College
South Street
St. Andrews
Fife KY16 9JP

Date: 04 March 2009
Your Ref:
Our Ref: **FB/LR/09/S1401/24**
Enquiries to: Miss Fiona Bain
Extension: Ninewells extension 32701
Direct Line: 01382 632701
Email. fionabain@nhs.net

Dear Mrs Johnston

Full title of study: **Long-term glycaemic control of diabetes and its relationship with cognitive function in type 1 diabetes mellitus.**

REC reference number: **09/S1401/24**

The Research Ethics Committee reviewed the above application at the meeting held on 27 February 2009. Thank you for attending to discuss the study.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

You clarified the following points:

- While carrying out the assessment the video recorder will only be pointing at the participants' hand and test sheet.
- Regarding A22 on the application form - You clarified that you were a registered Psychologist in Canada and had the experience to calm people by talking to them should the need arise.
- You clarified that if there were any plans for a follow up study it would be carried out by someone else as you only have a limited time here as a PhD student.

Please clarify the following points in letter form and submit revised Participant Information Sheet with version number and full date and any other documentation requested:

1. Regarding Application Form:
   - A27-5 has not been ticked, please clarify.

POSITIVE ABOUT DISABLED PEOPLE

2. Regarding Participant Information Sheet:

- You should state in the introductory paragraph that this is part of an educational qualification.
- Please adapt and include complaints paragraph:

  If you believe that you have been harmed in any way by taking part in this study, you have the right to pursue a complaint and seek any resulting compensation through the University of Dundee who are acting as the research sponsor. Details about this are available from the research team. Also, as a patient of the NHS, you have the right to pursue a complaint through the usual NHS process. To do so, you can submit a written complaint to the Patient Liaison Manager, Complaints Office, Ninewells Hospital (Freephone 0800 027 5507). Note that the NHS has no legal liability for non-negligent harm. However, if you are harmed and this is due to someone's negligence, you may have grounds for a legal action against NHS Tayside but you may have to pay your legal costs.

- Please include an independent contact should any participants have any queries. This should be someone within the department but not involved with the study.
- Please adapt and include the full paragraph regarding Tayside Committee on Medical Research Ethics i.e.

  The Tayside Committee on Medical Research Ethics, which has responsibility for scrutinising proposals for medical research on humans, has examined this proposal and has raised no objections from the point of view of medical ethics. It is a requirement that the research records are made available to monitors from NHS Tayside/and the Regulatory Authorities (the latter applicable ONLY in drug trials) whose role is to check that research is properly conducted and the interests of those taking part are adequately protected.

Ethical review of research sites

The favourable opinion applies to the research site listed on the attached form.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Statement of indemnity		11 August 2008
Letter of Invitation with Response Card	1	05 February 2009
CV Dr A J Astell		03 September 2008

Participant Consent Form	1	05 February 2009
Participant Information Sheet	1	05 February 2009
GP/Consultant Information Sheets	1	05 February 2009
Letter of invitation to participant	1	05 February 2009
Questionnaire: NART		
Questionnaire: HADS		
Questionnaire: The W-BQ28		15 January 2007
Questionnaire: Diabetes Questionnaire	1	05 February 2009
Questionnaire: Participant Inclusion/Exclusion Interview	1	05 February 2009
Covering Letter		05 February 2009
Protocol		05 February 2009
Investigator CV		
Application		06 February 2009
Questionnaire: Trail Making Test		
Questionnaire: RAVLT		

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

Appendix G

Cognitive Study: NHS Research and Development Approval

EC/LH

09 March 2009

Mrs Harriet Johnston
PhD Student
School of Psychology
St. Marys College
ST.ANDREWS
KY16 9JP

Dear Mrs Johnston,

NHS TAYSIDE MANAGEMENT/GOVERNANCE APPROVAL

R&D Project ID: 2009DM01

Title: Long-term Glycaemic Control of Diabetes and Its Relationship With Cognitive Function in Type 1 Diabetes Mellitus

Ethics Ref: 09/S1401/24 **Ethics Approval Date: 04/03/09**

Funder: Unfunded

Sponsor: University of St. Andrews

NHS Support Costs: £2,740

The above project has been registered on the NHS Tayside R&D database, as required by the Research Governance Framework. Full ethics approval has been obtained and there are £2,740 of local NHS Support Costs associated with this research project.

NHS Tayside has no objection to the project proceeding, provided all necessary approvals are in place and all amendments to the protocol, personnel involved and funding be notified to the R&D Office and all appropriate personnel.

It is important to note that all research must be carried out in compliance with the Research Governance Framework for Health & Community Care, GCP and the new EU Clinical Trials Directive (for clinical trials involving investigational medicinal products).

Kind Regards

Elizabeth Coote
Non-Commercial
R&D Manager

c.c. Mrs Lorraine Reilly (Assistant Administration Manager, NHS Tayside)
Mr Ian Robertson (Deputy Director of Finance, University of St.Andrews)
Dr John Petrie (Consultant Physician, NHS Tayside)

Appendix H

Cognitive Study UTREC Ethics Approval

University of St Andrews
[600 YEARS 1413 – 2013]

Harriet Johnston <hnj2@st-andrews.ac.uk>

PS5381_Approval

psyethics <psyethics@st-andrews.ac.uk> **14 April 2009 16:26**
To: hnj2@st-andrews.ac.uk
Cc: Arlene Astell <aja3@st-andrews.ac.uk>

14 April 2009

Ethics Reference No: ***Please quote this ref on all correspondence***	PS5381
Project Title:	Long-term glycaemic control of diabetes and its relationship with cognitive function in Type 1 diabetes mellitus
Researchers Name(s):	Harriet Naomi Johnston
Supervisor(s):	Dr A Astell

Thank you for submitting your application which was considered at the Psychology School Ethics Committee meeting on the 14 April 2009. The following documents were reviewed:

Ethical Application Form
Participant Information Sheet
Consent Form
External Permissions
Letters to Parents/Children/Headteacher etc…
Questionnaires
Enhanced Disclosure Scotland and Equivalent
(as necessary)

The University Teaching and Research Ethics Committee (UTREC) approves this study from an ethical point of view. Please note that where approval is given by a School Ethics Committee that committee is part of UTREC and is delegated to act for UTREC.

Approval is given for completion within the stated time period. Projects, which have not commenced within the time given must be re-submitted to your School Ethics Committee.

You must inform your School Ethics Committee when the research has been completed. If you are unable to complete your research within the validation period, you will be required to write to your School Ethics Committee and to UTREC (where approval was given by UTREC) to request an extension or you will need to re-apply.

Any serious adverse events or significant change which occurs in connection with this study and/or which may alter its ethical consideration, must be reported immediately to the School Ethics Committee, and an Ethical Amendment Form submitted where appropriate.

Approval is given on the understanding that the 'Guidelines for Ethical Research Practice' (http://www.st-andrews.ac.uk/media/UTRECguidelines%20Feb%2008.pdf) are adhered to.

Yours sincerely

On behalf of the Convenor of the School Ethics Committee OR Convener of UTREC

Appendix I

Cognitive Study: Diabetes Questionnaire

Participant ID Number _____ Age _____

Gender M / F (circle)

How many years of formal education have you taken from the time you started primary school?

_____

Year of diabetes diagnosis _____

Age at diabetes diagnosis _____

How many hypoglycaemic events have you experienced that have required assistance or hospitalization? (estimate number per year if frequent occurrence)

Total number = _ ____ OR Estimate of number per year = _____

How many hypoglycaemic comas have you experienced and when did these occur? Include total number? (estimate number per year if frequent occurrence)

Total number = ____ OR Estimate of number per year = ____

What medications or types of medications do you use currently?

_____

Do you have any other medical conditions? If so list

_____

What is your level of physical activity compared to others of your age?

Circle One

Much Less Less Same As More Much More

What is your level of cognitive activity (e.g. work, school, puzzles, reading) compared to others of your age? Circle One

Much Less Less Same As More Much More

Appendix J

Cognitive Study: Follow-Up Interview

Are you a smoker?

Current __ Past__ Never___

You said you exercise (much less, less, same as, more, much more) than other people your age. What type of exercise do you do? How much and how often per week?

Over the last 2 weeks what was your highest exertion level out of all your physical activities. Rate of perceived exertion is how hard you think your body is working based on increased heart rate, increased breathing rate, increased sweating and muscle fatigue

__ 0 - Nothing at all

__ 1 - Very light (gentle walking – 50% effort)

__ 2 - Light (60% effort)

__ 3 - Moderate

__ 4 - Some what strong (70% effort – steady pace)

__ 5 – strong (80% effort)

__ 6

__ 7 - Very strong (90% effort)

__ 8

__ 9

__ 10 - Very, very strong - maximal (100% effort)

You said you do (much less, less, same as, more, much more) cognitive or thinking activities than others your age. What type of thinking activities do you do? How much and how often per week?

Do you drink alcohol ?

Yes ___ No ___

How much per week? _____

Waist ____ Hip _____

Current Blood glucose ____

Appendix K

Method of Frequency Weighted Mean and Standard Deviation HbA1c Calculation

First, a method was operationalized to deal with duplicate information on the SCI-DC record. Due to the possibility of clerical errors leading to improbable values and duplication of values on SCI-DC (McAlpine, October 21, 2009) the HbA1c values needed to be checked and corrected for potential errors. First the record of individual HbA1c scores was cleaned (i.e. removing duplicates values recorded on the same day, removing dates with no recorded values, and removing improbable values). An improbable value was considered an HbA1c value that was at or below the lower limit (≤4%) of the normal range of HbA1c for a person without diabetes (4 to 6%). The target HbA1c for someone with diabetes is 6.5 to 7.5% (Diabetes UK, 2011b). If different values were recorded for the same day, the higher of these values was retained to be consistent with local convention detailed in an email communication by the Managed Care Network (MCN) Data Facilitator for SCI-DC (McAlpine, October 21, 2009). When different values were recorded for the same week all values were retained and weighted by the number of days between readings. In this way a reading a few days apart has less weight in the overall mean than readings that are months apart. This was done to reduce the potential for loss of actual HbA1c values in the data cleaning process.

Next the frequency of the records was determined for each value. This was number of months or part months between the mid

point of one reading and the midpoint of the next. If the absolute number of months between readings was used, this would leave the first reading with no weighting. Therefore to be able to assign a weight to the first reading it was assumed that the number of days between first HbA1c value and the one preceding it would approximately be the same as the actual number of days between the first and second HbA1c readings. It was then also necessary to estimate the number of days between the last reading and the next reading which was assumed to be the same as the number of days between the second-last and last reading. In this way an estimated weight based on the days between one actual or dummy reading and the next reading was assigned for each HbA1c value as illustrated in the following table.

Method to determine frequency weighting for HbA1c values

HbA1c Record No.	1	2	3	4	5	6	7	8	9	10	11	12
Days from last record	0	X1	X2	X3	X4	X5	X6	X7	X8	X9	X10	0
Mid point of days between records	$X2-\frac{X1}{2}$	$X2-\frac{X1}{2}$	$X3-\frac{X2}{2}$	$X4-\frac{X3}{2}$	$X5-\frac{X4}{2}$	$X6-\frac{X5}{2}$	$X7-\frac{X6}{2}$	$X8-\frac{X7}{2}$	$X9-\frac{X8}{2}$	$X10-\frac{X9}{2}$	$X11-\frac{X10}{2}$	$X11-\frac{X10}{2}$

N.B. shaded boxes indicate HbA1c values for which months between readings was estimated

Finally, the frequency weighted mean HbA1c was calculated. Each HbA1c value was multiplied by the value for days between readings. These values were then summed and divided by the sum of days

between readings. These values were also used to determine a frequency weighted standard deviation of HbA1c scores shown in the following equations.

$$\text{Frequency Weighted Mean} = \frac{\sum x_i w_i}{\sum w_i}$$

x= HbA1c Value ; w= Number of days between readings

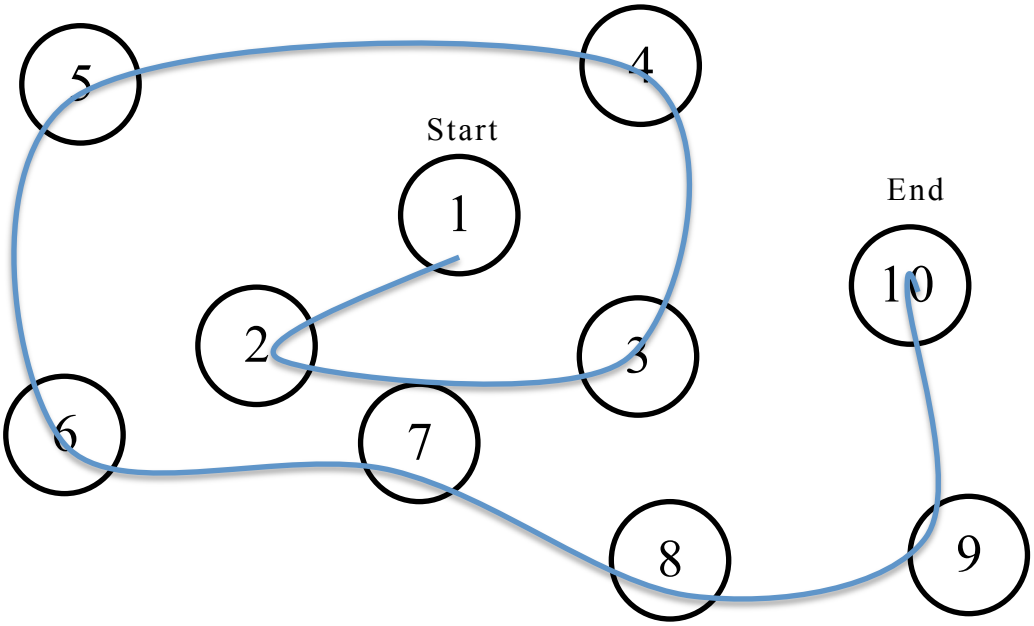
$$\text{Frequency Weighted SD} = \frac{\sum x_i^2 w_i}{\sum w_i / n}$$

x= HbA1c Value ; w= Number of days between readings; n=number of readings

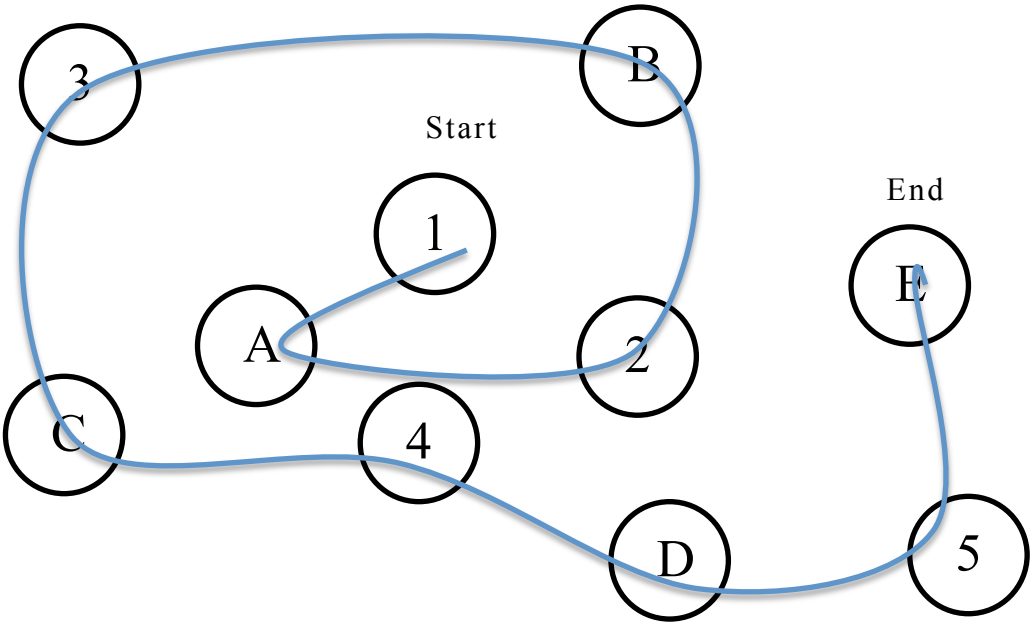
Appendix L

Sample Items for Cognitive Tests in a Visual Format

Trail Making A – Sample



Trail Making B – Sample



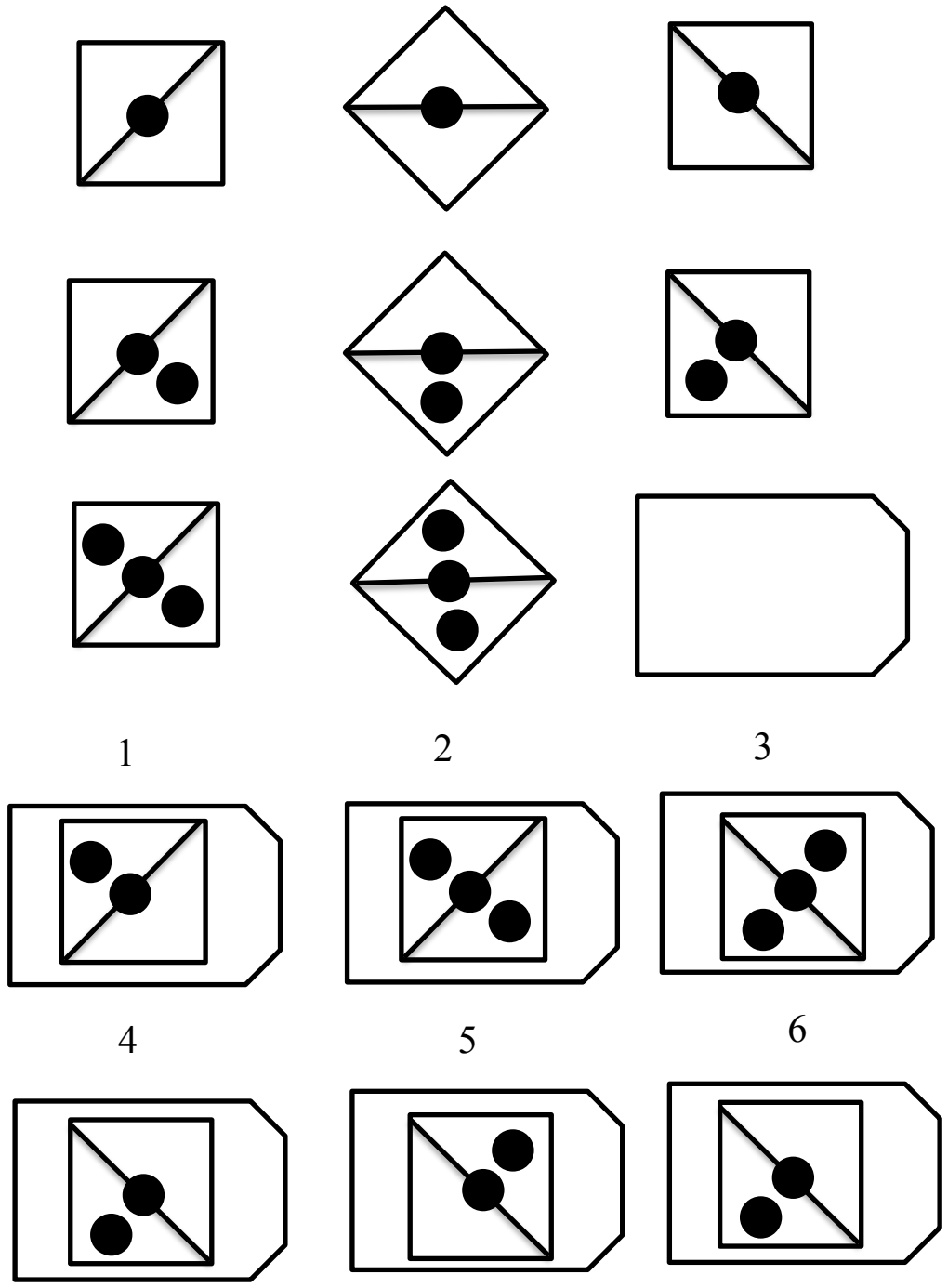
Symbol Digit Modalities Test - Sample

KEY

X	±	O	Δ	=	«	~	¬	—
1	2	3	4	5	6	7	8	9

¬	X	O	«	Δ	¬	=	~	X	—	±	¬
8	1	3	6	4	8	5	7				

Raven's Standard Progressive Matrices – Sample



Appendix M

Cognitive Test Raw Score to Standard Score Conversion

Cognitive Test	Raw Score	Standard Score Conversion
Symbol Digit Modalities Test: Written	Number items correctly written within 90 second time limit. Maximum score 110	Z score calculated based on mean and standard deviation for age and years of education (Smith, 1982)
Symbol Digit Modalities Test: Written	Number items correctly spoken within 90 second time limit. Maximum score 120	Z score calculated based on mean and standard deviation for age and years of education (Smith, 1982)
Trail Making Test (A&B)	Seconds to complete	Z score calculated based on mean and standard deviation for age (Spreen & Strauss, 1998).
NART-IQ	Number of errors in 50 items	Errors converted to WAIS Full Scale IQ score equivalent using NART-2 Conversion table (Nelson & Willison, 1991)
Ravens Standard Progressive Matrices (Ravens SPM)	Total correct in 20 minute time limit. Maximum = 60	Used in calculation of ELCC
Estimated Lifetime Cognitive Change (ELCC)	NART-2 number correct and Ravens SPM number correct in 20 minutes	Standardized residual (z score) - regression-based difference to adjust current ability (Ravens SPM) for prior ability (NART-2; Deary, Whalley, and Crawford, 2004)
Age-Adjusted Estimated Lifetime Cognitive Change (A-ELCC)	ELCC and Participant Age	Standardized residual (z score) regression-based difference to adjust ELCC for participant age
AMIPB Story Recall Immediate (SRI)	Number of story ideas recalled correctly immediately after hearing a story. 28 ideas maximum 2 points/idea maximum score = 58	Z score calculated based on mean and standard deviation for age (Coughlan & Hollows, 1985)
AMIPB Story Recall Delayed (SRD)	Number of story ideas recalled correctly 30 minutes after hearing a story 28 ideas maximum 2 points/idea maximum score = 58	Z score calculated based on mean and standard deviation for age (Coughlan & Hollows, 1985)
AMIPB Story Recall Retained	(SRD/SRI) X 100	Z score calculated based on mean and standard deviation for age (Coughlan & Hollows, 1985)

Table M (cont.)

Cognitive Test	Raw Score	Standard Score Conversion
Digit Span Forward (DSF)	DSF Total Score number correct of 8 Trials x 2 Items/Trial Maximum = 16	
Digit Span Backward (DSB)	DSB Total Score = number correct of 8 Trials x 2 Items/Trial Maximum = 14	
Digit Span	DS Scaled Score = DSF Total Score + DSB Total Score. Maximum 30	Z score calculated based on mean and standard deviation for scaled scores (Wechsler, 1997)

Appendix N

Required Transformations for Normalization Of Study Variables

To preserve the variable and number of data points for each analysis transformations were tried in the following order

1. Variable Transformation

log 10 (Log) , square root (SQRT) and reciprocal (Rec) transformation

2.Minimizing Outliers

If an outlier was ≥3SD from the mean, the score was changed to mean + 2.5, 3.0 or 3.5 SD if transformation failed as long as the relative position of the outlier was maintained (i.e. did not change positions with the next nearest score).

3. Non-parametric Statistics

Used if transformations and minimizing outliers failed.

The results of the successful transformation are shown in the following table. A transformation was considered successful if the distribution looked normal and the z values for skewness and kurtosis were below 2 SD above the mean as recommended by Field (2005). If transformation and minimizing outliers did not normalize the distribution,

non-parametric statistics were used

Table N.1

Check for Normal Distribution of Cognitive Test Variables and Required Transformation

Variable	Pre-Transformation								Post-Transformation					
	Skewness (*S*)			Kurtosis (*K*)			Outlier	Transformation	Skewness (*S*)			Kurtosis (*K*)		
	S	*SE*	*zS*	*K*	*SE*	*zK*	≥3SD	Transformation/Minimize Outlier	*S*	*SE*	*zS*	*K*	*SE*	*zK*
Adj-LCC	-.71	.249	-2.8	1.8	.493	3.7	z=-3.7	Changed outlier value to mean +2.5 SD =-2.49 (TAdj_Cog_Change)	-.42	.249	1.7	.80	.493	1.6
TMT-AZ	1.5	.249	6.1	4.6	.495	9.2	z=4.2	Changed outlier value to mean +3.5 SD = 3.09 & SQRT Transformation (SQRTT_TMTAZ)	-.118	.250	.47	.85	.495	1.7
TMT-BZ	1.4	.249	5.5	1.9	.495	3.8	z=4.3 z=4.2	Changed outlier values to mean + 3 SD =3.82 & SQRT Transformation (SQRTT_TMTBZ)	.33	.249	1.3	.30	.495	.61
SRI-Z	-.08	.249	-0.3	-.15		-0.3								
SRD-Z	-.23	.249	-0.9	-.32		-0.7								
SRR-Z	-.55	.249	-2.2	2.0	.493	4.1		Non-parametric						
SDMTWZ	.03	.249	.12	-.05		-0.1								
SDMTOZ	.12	.249	.47	.16		.31								
DS-Z	.56	.249	2.3	.07	.493	.13		SQRT Transformation (SQRT_DS_ScaleZ)	-.18	.249	.73	.13	.493	.27
NART IQ	-.75	.249	-3.0	.65	.493	1.3		Reverse and SQRT Transformation (SQRT_RIQ)	-.25	.249	.99	.30	.493	.60
Education	.679	.249	2.73	.011	.493	.022		Non-parametric						

N.B. Adj-LCC: Age-Adjusted Lifetime Cognitive Change; TMT-AZ: Trail Making Test A z-Score; TMT-BZ: Trail Making Test B z-Score; SRI-Z: Story Recall Immediate z-Score; SRD-Z: Story Recall Delayed z-Score; SRR-Z: Story Recall Retained z-Score; SDMT W-Z: Symbol Digit Modalities Test Written z-Score; SDMT O-Z: Symbol Digit Modalities Test Oral z-Score; DS-Z: Digit Span z Score. Because TMT values are counter-intuitive (a higher score indicates poorer performance) both TMT variables were reversed after transformation when used in the statistical analysis to be in alignment with the direction of the other cognitive variables.

Table N.2

Check for Normal Distribution of Demographic and Diabetes & Health Variables and Required Transformation

Variable	Pre-Transformation								Post-Transformation					
	Skewness (*S*)			Kurtosis (*K*)			Outlier	Transformation	Skewness (*S*)			Kurtosis (*K*)		
	S	*SE*	*zS*	*K*	*SE*	*zK*	z	Transformation/Minimize Outlier	*S*	*SE*	*zS*	*K*	*SE*	*zK*
Age of Onset	.48	.249	1.94	-.002	.493	.004								
Duration of Diagnosis	.47	.249	1.89	-.072	.493	-.15								
Mean HbA1c	.41	.249	1.63	1.53	.495	3.08	3.0	Changed outlier value to mean + 3SD =11.2 (TMean_HbA1c)	.12	.250	0.48	.39	.495	0.79
Insulin Resistance (eGDR)	.91	.251	3.65	.251	.498	0.50	2.4	Log Transformation (Log eGDR)	.034	.251	0.14	.150	.498	0.30
Age	.47	.249	1.96	-.49	.493	1.0								
Microvasc. Disease	.934	.249	3.75	.714	.493	1.45	4.6	Square Root Transformation (SQRT_Micro)	-.267	.249	-1.07	.668	.493	1.35
BMI	.587	.249	2.36	.072	.493	0.15	3.1	Log Transformation (Log BMI)	.252	.249	1.01	-.397	.493	-0.81
Waist-Hip Ratio	-.15	,251	-0.60	-.731	.498	-1.47								
Diastolic	-.013	.249	-0.05	.000	.493	0								
Systolic	.335	.249	1.36	.035	.493	0.07								

Table N.2 (cont.)

Variable	Pre-Transformation								Post-Transformation					
	Skewness (*S*)			Kurtosis (*K*)			Outlier	Transformation	Skewness (*S*)			Kurtosis (*K*)		
	S	*SE*	*zS*	*K*	*SE*	*zK*	z	Transformation/Minimize Outlier	*S*	*SE*	*zS*	*K*	*SE*	*zK*
Cholester.	.569	.249	2.29	.061	.493	0.12	2.7	SQRT Transformation (SQRT Choles)	.349	.249	1.40	-.207	.439	-0.47
HDL	.439	.249	1.76	-.064	.493	-.013								
Cholester Ratio	.901	.249	3.62	.554	.439	1.26	3.4	Log Transformation (Log CholRatio)	.264	.249	1.06	-.490	.439	-1.12
Tri-glycerides	1.76	.249	7.07	3.82	.493	.748	4.1	Log Transformation (Log Trig)	.294	.249	.181	-.094	.493	-0.19

NB Microvasc. Disease: Microvascular Disease combined rating of severity retinopathy, neuropathy and nephropathy; Cholester.= Total Cholesterol; HDL = HDL Cholesterol; Cholester. Ratio = Cholesterol Ratio (Total Cholesterol/HDL Cholesterol

Appendix O

Cognitive Study Correlation Tables

Table O.1

Correlation between Demograhphic and Diabetes Health Variables

Variable	Duration of Diagnosis	Age at Onset	HbA1c Current	Mean HbA1c	HbA1c Recent	HbA1cSD	Highest Retinopathy	Micro Total	Insulin Resistance (eGDR)	Hypo Help
Age	.381 (.000)**	.271 (.004)**	-.011 (.46)	.099 (.17)	.028 (.40)	-.076 (.23)	.276 (.004)**	.310 (.001)**	-.035 (.37)	.000 (.50)
Education	-.083 (.21)	.077 (.23)	-.223 (.02)*	-.145 (.08)	-.191 (.03)*	-.113 (.14)	-.142 (.09)	-.227 (.014)*	.048 (.33)	-.138 (.09)
Gender (Female)	.137 (.093)	-.120 (.13)	-.017 (.44)	.068 (.26)	.058 (.29)	.072 (.25)	-.002 (.49)	-.056 (.30)	.571 (.000)**	-.008 (.47)
NART IQ	-.040 (.31)	.190 (.03)*	-.237 (.011)*	-.143 (.09)	-.167 (.054)	-.209 (.02)*	-.047 (.33)	-.199 (.03)*	.140 (.091)	-.097 (.18)

Spearman's rho one-tailed significance used *p<.05, **p<.01

Level of insulin resistance based on estimated glucose disposal rate (eGDR) – higher eGDR is related to lower insulin resistance

Table O.2

Correlation of Diabetes Health Variables with Cognitive Tests

Variable	Age-Adjusted Cog Change	TMTA	TMTB	SRI	SRD	SRR	SDMT-W	SDMT-O	Digit Span
Duration of Diagnosis[a]	-.034 (.37)	-.205 (.02)*	-.238 (.01)*	.088 (.20)	.051 (.31)	-.033 (.38)[b]	-.125 (.12)	-.172 (.049)*	-.016 (.44)
Age of Onset[a]	.038 (.36)	.123 (.12)	.126 (.11)	-.088 (.20)	-.080 (.22)	-.020 (.43)[b]	.067 (.26)	.059 (.29)	.096 (.18)
Insulin Resistance (eGDR)[a]	-.008 (.47)	-.094 (.19)	-.039 (.36)	.063 (.28)	.077 (.23)	.137 (.10)[b]	.079 (.23)	.036 (.37)	.024 (.41)
Hypo Help[b]	-.106 (.15)	-.077 (.23)	-.046 (.33)	-.026 (.40)	.000 (.50)	.086 (.21)	-.007 (.47)	.043 (.34)	-.102 (.16)
Highest Retionopathy[b]	-.188 (.04)*	-.227 (.014)**	-.187 (.04)*	.016 (.44)	-.024 (.41)	-.154 (.070)	-.152 (.07)	-.168 (.054)	.109 (.15)
Microvascular Total[a]	-.209 (.02)*	-.258 (.006)**	-.264 (.005)**	-.023 (.41)	-.099 (.17)	-.190 (.03)[b]*	-.307 (.001)**	-.275 (.004)**	-.063 (.27)
Mean HbA1c[a]	-.171 (.051)	.006 (.48)	.010 (.46)	.091 (.19)	.044 (.34)	-.150 (.08)[b]	-.052 (.31)	-.014 (.45)	.005 (.48)
HbA1c Recent[a]	-.141 (.09)	.064 (.27)	.050 (.32)	.172 (.049)*	.105 (.16)	-.153 (.07)[b]	.048 (.33)	.044 (.34)	-.016 (.44)
HbA1c Current[a]	-.125 (.11)	.098 (.18)	-.047 (.33)	.186 (.02)*	.150 (.07)	-.156 (07)[b]	-.011 (.48)	-.026 (.40)	-.080 (.22)
Glucose on Test Date[a]	-.136 (.10)	-.052 (.32)	-.252 (.008)**	-.058 (.29)	-.076 (.24)	-.036 (.37)[b]	-.093 (.19)	-.070 (.26)	-.220 (.018)*
HbA1c SD[a]	-.079 (.23)	.024 (.41)	.025 (.41)	-.005 (.48)	-.044 (.34)	-.024 (.41)[b]	-.065 (.27)	-.006 (.48)	-.089 (.20)

a. Pearson's correlation one-tailed used*p<.05, **p<.01

b. Spearman's rho one-tailed used*p<.05, **p<.01

TMT correlations were reversed for ease of comparison with other cognitive tests

Level of insulin resistance based on estimated glucose disposal rate (eGDR) – higher eGDR is related to lower insulin resistance

Table O.3
Correlation between Diabetes Health Variables

Variable	Mean HbA1c	HbA1c Recent	HbA1c Current	Glucose on Test Date	HbA1cSD	Duration of Diagnosis	Age at Diagnosis	Insulin Resistance (eGDR)	Highest Retinopathy	Microvascular Total
HbA1c Recent[a]	.826 (.000)**									
HbA1c Current[a]	.580 (.000)**	.794 (.000)**								
Glucose On Test Date[a]	.273 (.005)**	.282 (.003)**	.249 (.009)							
HbA1c SD[a]	.492 (.000)**	.373 (.000)*	.181 (.040)	.261 (.006)**						
Duration of Diagnosis[a]	.050 (.32)	-.020 (.42)	.003 (.49)	.176 (.048)*	.138 (.09)					
Age of Onset[a]	.024 (.41)	.029 (.39)	-.002 (.49)	-.174 (.049)*	-.230 (.013)*	-.715 (.000)**				
Insulin Resistance (eGDR)[a]	-.292 (.002)**	-.390 (.000)**	-.500 (.000)**	-.167 (.058)	-.119 (.129)	.001 (.50)	-.034 (.37)			
Highest Retinopathy[b]	.365 (.000)**	.333 (.001)**	.274 (.004)**	.073 (.25)	.080 (.223)	.367 (.000)**	-.148 (.08)	-.311 (.001)**		
Microvascular Total[a]	.470 (.000)**	.350 (.000)**	.202 (.026)**	.103 (.17)	.156 (.067)	.345 (.000)**	-.145 (.08)	-.320 (.001)**	.817 (.000)**	
Hypo Help[b]	-.056 (.30)	-.010 (.46)	.149 (.08)	-.249 (.009)**	.040 (.35)	-.011 (.46)	-.044 (.34)	.033 (.38)	-.059 (.29)	.042 (.34)

a.Pearson's one-tailed significance used *p<.05, **p<.01
b.Spearman's rho one-tailed significance used *p<.05, **p<.01
Level of insulin resistance based on estimated glucose disposal rate (eGDR) – higher eGDR is related to lower insulin resistance

Table O.4

Correlation between General Health Variables and Cognitive Tests

Variable	NART-IQ	TMTA	TMTB	SRI	SRD	SDMT-W	SDMT-O	Digit Span	Age-Adjusted Cognitive Change
Waist-Hip Ratio	-.060 (.28)	.164 (.06)	.095 (.19)	-.170 (.05)	-.177 (.046)*	-.040 (.35)	-.016 (.44)	-.035 (.37)	.103 (.17)
Body Mass Index	-.114 (.14)	.077 (.23)	.103 (.16)	-.159 (.06)	-.135 (.10)	.084 (.21)	.097 (.18)	.018 (.43)	-.126 (.11)
Systolic BP	-.038 (.36)	-.069 (.26)	-.013 (.45)	-.100 (.17)	-.105 (.18)	-.107 (.15)	-.058 (.29)	-.060 (.28)	.048 (.32)
Diastolic BP	.013(.45)	.161 (.06)	-.023 (.41)	-.091 (.19)	-.058 (.29)	.023 (.41)	-.006 (.48)	-.051 (.31)	.052 (.31)
High BP	-.057 (.29)	-.099 (.17)	-.011 (.46)	-.077 (.23)	-.108 (.15)	-.051 (.32)	-.043 (.34)	-.036 (.37)	.006 (.48)
Total Choles	.000 (.50)	.120 (.13)	-.038 (.36)	.016 (.44)	.011 (.46)	.071 (.25)	-.009 (.47)	-.096 (.18)	-.082 (.22)
HDL	.037 (.36)	-.041 (.35)	-.037 (.36)	.152 (.07)	.144 (.08)	.048 (.32)	.054 (.31)	-.175 (.046)*	.008 (.47)
Total/HDL Ratio	-.035 (.37)	.099 (.17)	.021 (.42)	-.099 (.17)	-.100 (.17)	-.004 (.49)	-.055 (.30)	.096 (.18)	-.045 (.33)
Triglycerides	-.061 (.28)	.056 (.30)	.070 (.25)	-.114 (.14)	-.128 (.11)	-.071 (.25)	-.047 (.33)	.133 (.10)	.034 (.37)
RPE	-.021 (.42)	.074 (.25)	.088 (.21)	-.070 (.26)	.031 (.39)	-.044 (.35)	.091 (.21)	.082 (.23)	.237 (.02)*
Exercise	.037 (.36)	.135 (.10)	.123 (.12)	.031 (.38)	.082 (.22)	.007 (.47)	.053 (.31)	.120 (.13)	.161 (.06)
Cognitive Activity	.182 (.04)*	.071 (.25)	.108 (.15)	.036 (.37)	.089 (.20)	.093 (.19)	.104 (.16)	.222 (.02)*	.118 (.13)

Spearman's rho one-tailed significance used *p<.05

TMT correlations were reversed for ease of comparison with other cognitive tests

RPE: Rate of Perceived Exertion in exercise on a scale of 0 (no effort) to 10 (maximal effort)

Exercise: Self-rating in comparison to age peers – Less Exercise (0), Same Exercise (1), More Exercise (2)

Cognitive Activity: Self-rating in comparison to age peers – Less Cognitive Activity (0), Same Cognitive Activity (1), More Cognitive Activity (2)

Total Choles: Total Cholesterol; HDL – High-density lipoprotein (higher scores indicate better health);

High BP : Systolic >140 and or Diastolic >90

Appendix P

Correlation of Psychological Variables with Demographics, Diabetes Health, and Cognitive Function

Table P.1
Inter-correlations between HADS and WBQ scores

	HADS A	HADS D	GNWB	GE	GPWB	GS	DNWB	DS	DPWB	GWB
HADS-Depress	.631									
WBQ General Negative Well-Being (GNWB)	.702	.486								
WBQ General Energy (GE)	-.462	-.645	-.529							
WBQ General Positive Well-Being (GPWB)	-.492	-.702	-.517	.673						
WBQ General Stress (GS)	.660	.503	.644	-.480	-.540					
WBQ Diabetes Negative Well-Being (DNWB)	.550	.458	.502	-.390	-.417	.436				
WBQ Diabetes Stress (DS)	.485	.449	.401	-.352	-.367	.424	.674			
WBQ Diabetes Positive Well-Being (DPWB)	-.387	-.409	-.266	.420	.494	-.194	-.451	-.371		
WBQ General Well-Being (GWB)	-.681	-.718	-.767	.815	.843	-.817	-.515	-.446	.416	
WBQ Diabetes Well-Being (DWB)	-.531	-.480	-.438	.456	.530	-.410	-.819	-.766	.788	.546

Spearman's rho one-sided correlation values. All values significant at $p<.01$

Table P.2

Correlation of Psychological Variables with Demographic and Diabetes Health Variables

Variable	Age	Education	Gender	Duration of Diagnosis	Age of Onset	Hypo Help	Insulin Resist (eGDR)	Highest Retinopathy	Microvascular Total	Mean HbA1c	Recent HbA1c	Current HbA1c
HADS-Anxiety	-.289	-.003	-.154	-.106	-.095	.162	.280	-.288	-.260	-.025	-.073	-.049
	(.002)**	(.490)	(.070)	(.15)	(.18)	(.06)	(.003)**	(.002)**	(.006)**	(.41)	(.24)	(.32)
HADS-Depress	-.143	-.170	-.077	-.079	-.074	.092	.103	-.185	.003	.187	.107	.097
	(.09)	(.051)	(.23)	(.23)	(.23)	(.19)	(.17)	(.038)*	(.49)	(.036)*	(.15)	(.18)
WBQ General Negative Well-Being	-.327	.087	-.265	-.053	-.176	.045	.267	-.170	-.205	-.016	-.022	-.096
	(.001)**	(.20)	(.005)**	(.31)	(.043)*	(.36)	(.005)**	(.050)	(.024)*	(.44)	(.42)	(.18)
WBQ General Energy	.302	.111	.120	.071	.174	-.090	-.101	.156	.078	-.073	-.153	-.082
	(.002)**	(.14)	(.12)	(.25)	(.047)*	(.19)	(.17)	(.067)	(.23)	(.24)	(.070)	(.22)
WBQ General Positive Well-Being	.304	.215	.118	.134	.103	-.121	-.064	.214	.042	-.081	-.091	-.082
	(.001)**	(.019)*	(.13)	(.10)	(.16)	(.12)	(.27)	(.019)*	(.34)	(.22)	(.19)	(.22)
WBQ General Stress	-.393	.085	-.149	-.041	-.249	.031	.183	-.241	-.173	.112	.017	.020
	(.000)**	(.21)	(.08)	(.35)	(.008)**	(.38)	(.040)*	(.010)*	(.048)*	(.14)	(.44)	(.43)
WBQ Diabetes Negative Well-Being	-.243	-.087	-.180	-.073	-.067	.104	.131	-.068	.020	.131	.149	.089
	(.008)*	(.20)	(.041)*	(.24)	(.26)	(.16)	(.11)	(.26)	(.42)	(.11)	(.075)	(.20)
WBQ Diabetes Stress	-.129	.053	-.033	-.060	-.036	.008	.102	-.047	.025	.222	.181	.101
	(.108)	(.31)	(.38)	(.30)	(.37)	(.47)	(.17)	(.33)	(.41)	(.016)*	(.040)*	(.17)
WBQ Diabetes Positive Well-Being	.239	.088	.063	.253	-.082	-.122	-.114	.117	.104	-.133	-.182	-.176
	(.010)*	(.20)	(.27)	(.007)*	(.22)	(.14)	(.14)	(.13)	(.16)	(.10)	(.039)*	(.045)*
WBQ General Well-Being	.406	.044	.161	.109	.199	-.064	-.149	.250	.150	-.090	-.081	-.055
	(.000)**	(.34)	(.061)	(.15)	(.03)*	(.27)	(.08)	(.007)**	(.075)	(.20)	(.22)	(.30)
WBQ Diabetes Well-Being	.264	.044	.127	.149	.025	-.103	-.135	.109	.049	-.174	-.204	-.152
	(.005)*	(.34)	(.11)	(.08)	(.41)	(.16)	(.10)	(.15)	(.32)	(.048)*	(.024)*	(.07)

Spearman's rho one-tailed significance level indicated *p<.05, **p<.01

Level of insulin resistance is based on estimated glucose disposal rate (eGDR) – higher rating of eGDR is related to lower insulin resistance Gender: Female (0) Male (1)

Table P.3
Correlation of Psychological Variables with Cognitive Tests

Variable	NART IQ	TMT A	TMT B	Story Recall Immediate	Story Recall Delayed	Symbol Digit Written	Symbol Digit Oral	Digit Span	Age-Adjusted Cognitive Change
HADS-Anxiety	-.102	.085	-.042	-.079	.002	.110	.137	-.114	-.180
	(.16)	(.21)	(.34)	(.23)	(.49)	(.15)	(.09)	(.14)	(.04)*
HADS-Depress	-.219	.103	-.112	-.028	-.048	-.072	-.033	-.274	-.145
	(.02)*	(.16)	(.14)	(.40)	(.32)	(.25)	(.38)	(.008)**	(.08)
WBQ	-.059	-.060	-.041	-.069	-.006	.059	.037	-.111	-.255
General Negative	(.29)	(.28)	(.35)	(.26)	(.48)	(.29)	(.36)	(.14)	(.007)**
Well-Being									
WBQ	.175	.067	.111	.042	.051	.030	-.007	.215	.175
General Energy	(.045)*	(.26)	(.14)	(.34)	(.31)	(.39)	(.47)	(.02)*	(.046)*
WBQ	.222	.078	.063	.066	.049	.028	-.068	.256	.104
General Positive	(.016)*	(.23)	(.27)	(.27)	(.32)	(.40)	(.26)	(.006)**	(.16)
Well-Being									
WBQ	-.122	-.017	-.015	-.005	.048	-.054	-.010	-.048	-.243**
General Stress	(.12)	(.44)	(.44)	(.49)	(.32)	(.30)	(.46)	(.32)	(.009)
WBQ	-.144	-.027	-.220	.038	.056	-.002	.031	-.145	-.221
Diabetes	(.08)	(.40)	(.02)*	(.36)	(.30)	(.49)	(.39)	(.08)	(.016)*
Negative									
Well-Being									
WBQ	.078	.015	-.087	.062	.094	.034	.105	.051	-.112
Diabetes Stress	(.23)	(.44)	(.21)	(.28)	(.18)	(.37)	(.16)	(.31)	(.14)
WBQ	.028	.036	.072	-.039	-.042	-.086	-.098	.118	.109
Diabetes Positive	(.39)	(.37)	(.25)	(.35)	(.34)	(.21)	(.18)	(.13)	(.15)
Well-Being									
WBQ General	.190	.061	.074	.038	.010	.045	-.015	.196	.235
Well-Being	(.03)*	(.28)	(.25)	(.36)	(.46)	(.33)	(.44)	(.03)*	(.01)*
WBQ	.047	.057	.162	-.046	-.079	.024	-.060	.124	.214
Diabetes	(.33)	(.29)	(.06)	(.33)	(.22)	(.41)	(.28)	(.12)	(.02)*
Well-Being									

Spearman's rho one-tailed significance indicated *p<.05, **p<.01
TMT correlations were reversed for ease of comparison with other cognitive tests

Appendix Q
fMRI Ethics Documentation

NHS Fife NHS Forth Valley NHS Tayside

East of Scotland Research Ethics Service

Tayside Committee on Medical Research Ethics A
Research Ethics Office
Tayside Academic Health Sciences Centre
Ninewells Hospital & Medical School
Residency Block, Level 3
George Pirie Way
Dundee
DD1 9SY

Mrs Harriet Johnston
PhD Student
University of St. Andrews
St. Mary's
South Street
St. Andrews, Fife
KY16 9JP

Date: 03 September 2010
Your Ref:
Our Ref: FB/LR/10/S1401/40
Enquiries to: Miss Fiona Bain
Extension: Ninewells extension 02701
Direct Line: 01382 632701
Email: fionabain@nhs.net

Dear Mrs Johnston

Full title of study: **Long-term glycaemic control and its relationship with cognitive function in type 1 diabetes: A cognitive and neuroimaging Study**
REC reference number: **10/S1401/40**

The Research Ethics Committee reviewed the above application at the meeting held on 27 August 2010. Thank you and Dr Stephen Nicholas for attending to discuss the study.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

The following points require to be addressed by letter and submission of revised documentation where requested. **Please note that there is no requirement to amend your application form.**

1. Regarding the application form:
   - Regarding A57 – please clarify primary outcome as structural images and functional MRI data is not a primary outcome.
   - Please elaborate on sample size calculation in A60.
   - Regarding A2 – please confirm who the Chief Investigator is.
2. Regarding the Participant Information Sheet:
   - Please change title to include exploratory 'Thinking and Reasoning in Type 1 Diabetes: An Exploratory Neuroimaging Study'.

Please submit a revised Participant Information Sheet, which should include a new version number and new full date.

3. Regarding the Consent Form:

   - Please insert statement requesting permission to disclose any incidental findings if found.

Please submit a revised Consent Form, which should include a version number and full date as a footer and the new date and version number of Participant Information Sheet in Statement 1.

4. Thank you for giving me a copy of the updated insurance/indemnity policy at the meeting.

The following points were clarified on the application form:

- You clarified that you would not be using contrast and you would make it clear to participants that they understood that no contrast would be used.
- You clarified that you would not be excluding participants with insulin pumps as they are not MRI compatible. You did confirm that the pump can be taken off for up to an hour without putting participants at risk.
- You clarified that the structural MRI will be carried out by Professor Graeme Houston and you would be looking at different measure outcomes, differences in grey matter, different sizes of brain and different activation that looks like accelerated ageing to see if any difference in areas of good glycaemic control and poor glycaemic and to see if there are any age related effects. Dr Steve Nicholas will try to work out white matter volume and grey matter volume and look to see if there are any differences between the groups.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" **below**).

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk. Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Investigator CV		20 July 2010
Protocol	4	07 July 2010
CV - Dr Arlene Astell		06 August 2010
REC application		12 July 2010
Covering Letter		06 August 2010
Summary/Synopsis		
Letter of invitation to participant	1	20 July 2010
GP/Consultant Information Sheets	1	20 July 2010
Participant Information Sheet	2	20 July 2010
Participant Consent Form	1	15 June 2010
Questionnaire: MRI Patient Safety		
CV - Dr John Petrie		05 August 2010
Letter from Funder		25 February 2009
MRI Request Form		
Evidence of insurance or indemnity		01 July 2010

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

10/S1401/40	**Please quote this number on all correspondence**

Yours sincerely

Mr Carlos Wigderowitz
Chair

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments
"After ethical review – guidance for researchers"

Copy to: Ms Hana Polaskova
NHS Tayside R&D Office

Appendix R

fMRI Study Participant Information Sheet and Consent Form

Participant Information Sheet

Thinking and Reasoning in Type 1 diabetes: An Exploratory Neuroimaging Study

You are invited to participate in a research project. This research is part of an educational qualification. The following information is to help you decide if you want to take part. Read it carefully and discuss it with other people if you want. You can ask me any questions and I will do my best to answer them. Take time to decide whether or not you wish to take part.

What is the purpose of the study?
While much is known about the importance of blood glucose level control in diabetes for the maintenance of physical well being, recent evidence indicates that it may also be important in maintaining thinking and reasoning skills. The aim of this project is to find out whether blood glucose control levels and changes in blood vessel regulation may have a subtle impact on brain structure and function for individuals with diabetes.

Why have I been chosen?
This is a follow-up study of the same research question using cognitive tasks. You are invited to take part in this study because you took part in the cognitive component of this study.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the care you receive or affect your relationship with medical staff looking after you, now or in the future

What will happen if I decide to take part?
If you decide to take part you will have a magnetic resonance imaging (MRI) structural and functional scan at the Clinical Research Centre (CRC) at Ninewells Hospital, Dundee. The scan itself will take up to 60 minutes split into 2 sections, including a 45 minute brain MRI and a 15 minute MRI of a major blood vessel in the chest. The preparation for the scan (outside the scanner) can take up to 60 minutes as well. The total time required for the study will be a maximum of 2 hours for both the preparation and scanning time together. The structural and functional scans are completed together within this single session.

In preparation for the MRI scan, you will go through a safety questionnaire, and if you are considered safe to enter the MRI suite by the imaging staff, you will be given training on the different tasks you will be asked to complete while in the scanner. As you require an adequate glucose supply to perform your best on the cognitive tasks, before the scan you will be asked to take a blood glucose measurement (using your personal monitor) to ensure that you are not experiencing hypoglycaemia. If you are below 4 mmol/litre, glucose will be provided and a second glucose reading will be required to ensure you are ready to begin the cognitive tasks.

For those using external (removable) insulin pumps, please note that an insulin pump is not MRI safe and it must be removed before you enter the MRI scanner. For this study, that would be for a period of up to 60 minutes while you are in the MRI scanner. If you use a removable insulin pump and would like to take part in this study, please check with your physician. If removing the insulin pump for this period of time is not advised, it will not be safe for you to participate in this study.

Once these safety checks and training have been completed, you will then change into a hospital gown or scrubs and lie in an MRI scanner. You will be asked to lie very still during imaging. During the functional scans you will be asked to complete two thinking tasks, similar to the ones you completed in the "Thinking and Reasoning in Type 1 diabetes" study. During sections of the study we will ask you to perform these thinking tasks seen through goggles on a computer screen which require a finger button press response including:

- Responding to remembered letters
- Comparison of simple visual images

You will be given clear instructions and practice prior to going into the scanner on how to complete these tasks and you will be able to listen to and speak to the person carrying out your scan, who will remind you of what you have to do, before the scanning starts. The task instructions will also be presented for you to read right before the task begins.

What is Magnetic Resonance Imaging?
Magnetic Resonance Imaging (or MRI) uses a high strength magnetic field and non-ionising radiofrequency radiation to obtain images of the inside of the body. An MRI scanner looks a little like a CT scanner. MRI scans are painless, although it is possible that you might experience a minor amount of discomfort as a result of lying still on the MRI table.

What is fMRI?
Functional Magnetic Resonance Imaging (or fMRI) is a specific type of MRI scan which concentrates on the brain. It provides information about which parts of the brain are being used when people perform different tasks such as listening to noises, looking at pictures or patterns or performing simple mental tasks.

What are the possible disadvantages and risks of taking part?
The MRI scanner is loud and although you will be given earplugs to reduce the noise, you will still hear it. You must lie as still as possible during imaging. Some people find this uncomfortable and feel a little stiff

afterwards. If you experience feelings of claustrophobia, we suggest that you do not take part.

There are a number of safety hazards involved in entering an MR scanner. We reduce the risks involved as much as possible with our robust safety measures. These have ensured that NHS Tayside has provided a safe MRI service for over 10 years. Please speak to one of the people listed below if you would like more information. Your scan will be checked by a Consultant Radiologist. If an unexpected abnormality is discovered, it could have an impact on future applications that you make for mortgages, life insurance, health insurance or other services.

We do not anticipate any adverse effects from taking part in this study. If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

What are the possible benefits of taking part?
There are no direct advantages to you. However, we will make any future publications of the findings available to you. It is hoped that this research will improve our knowledge relating to Type 1 diabetes and may influence care practices and information provided to people with diabetes in the future. An anatomical image of your brain will be acquired and shown to a Consultant Radiologist. It is unlikely but possible that this image will reveal an abnormality that you were unaware of. Should this happen, the Consultant Radiologist will discuss the findings with you, inform your GP if necessary and recommend whether further investigations are appropriate or not.

What if you have any concerns or complaints?
Every reasonable precaution has been taken to ensure this research is conducted safely and effectively, in line with NHS good practice. However, you should feel free to direct any concerns or complaints to Dr. Arlene Astell (01334 462056) at the University of St Andrews who is supervising this project and who will liaise on your behalf with the other Higher Education and NHS bodies participating in the research. Should you have any immediate concerns whilst undergoing a scan, however, then please don't wait - raise them immediately with the NHS staff who are there to assist you. Of course, this does not supersede the usual NHS complaints processes, in which case you can also submit a written complaint to the NHS Tayside Patient Liaison Manager, Complaints Office, Ninewells Hospital, Dundee, or use Freephone number 0800 0275507. Whilst there is no legal liability for non-negligent harm arising from the study, this should not in any way deter you from using the above channels to register, discuss and resolve any problems, nor does it affect your legal rights in the event that anyone organising or carrying out the research is shown to be at fault.

What will happen to the information collected in the study?
All information collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognized from it. You will be allocated an anonymous ID code during

testing which will be used in place of your name on any future publications. Only group results or anonymous individual data will be communicated in Harriet Johnston's PhD thesis, research publications or at professional and public conferences.

Who is organizing and funding the research?
This research is being completed in fulfilment of PhD requirements for the School of Psychology at the University of St. Andrews. The research is supervised by Dr. Arlene Astell, a chartered clinical psychologist and lecturer at the University of St. Andrews, and Dr. Rory McCrimmon, a consultant physician at the Strathmore Diabetes Centre, NHS Tayside in collaboration with the other Diabetes Centres within NHS Tayside. Funding for neuroimaging is provided through an Anonymous Trust research award jointly held with Dr. Stephen Nicholas, MRI Physicist at the Clinical Research Centre and Professor Graeme Houston, Consultant Radiologist.

What happens now?
If you agree to take part you will be asked to complete a consent form. If you decide not to take part, this will have no bearing on your future care or treatment from the NHS. If you decide to take part we would like permission to inform your GP. However, if you do not agree to us informing your GP you can still take part. The Tayside Committee on Medical Research Ethics, which has responsibility for scrutinizing proposals for medical research on humans, has examined the proposal and has raised no objections from the point of view of medical ethics. It is a requirement that the research records are made available to monitors from NHS Tayside/and the Regulatory Authorities (the latter applicable ONLY in drug trials) whose role is to check that research is properly conducted and the interests of those taking part are adequately protected.

Contact for Further Information

Thank you for reading this information sheet. If you have any further questions feel free to contact Harriet Johnston at 01382 496483.

You may also contact Dr. Arlene Astell, who is the academic supervisor of this PhD research, for further information. You can reach Dr. Astell at 01334 462056.

Dr. Ewan Pearson, a consultant physician at Ninewells Hospital who is not involved in this study, is also available to provide an independent opinion about taking part. You can reach him at 01382 740081.

If you have understood the contents of this sheet and wish to take part, either contact Harriet Johnston by leaving a message at 01382 496483, or by email hjohnston1@nhs.net

Patient Identification Number:_____

CONSENT FORM

Title of Project: Thinking and Reasoning in Type 1 diabetes: An Exploratory Neuroimaging Study

Name of Researcher: Harriet Johnston

Please initial box

1. I confirm that I have read and understand the information sheet dated ..... (version __) for the above study and have had an opportunity to consider the information, the opportunity to ask questions, and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by the named researchers from the University of St. Andrews and from NHS Tayside where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to my GP being informed of my participation in the study. ☐

5. I agree to be informed of incidental findings if discovered on the MRI scan ☐

6.I agree to take part in the above study. ☐

_____ _____ _____

Name of Participant Signature Date

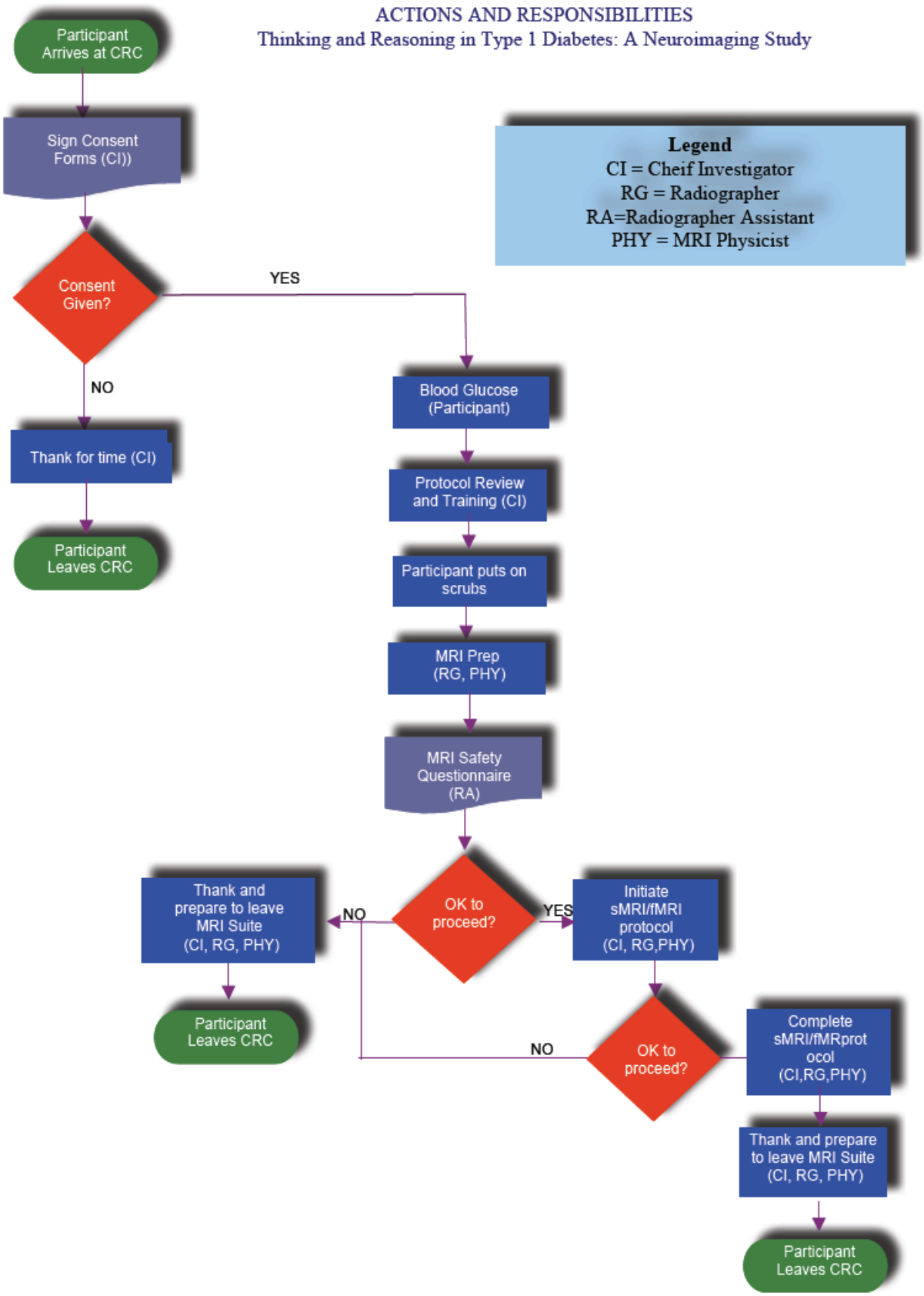
_

_____ _____ _____

Name of Person Taking Consent Signature Date

Appendix S

fMRI Study Procedure Flowchart


ACTIONS AND RESPONSIBILITIES
Thinking and Reasoning in Type 1 Diabetes: A Neuroimaging Study
Participant Arrives at CRC
Sign Consent Forms (CI))
Consent Given?
YES
NO
Thank for time (CI)
Participant Leaves CRC
Legend
CI = Cheif Investigator
RG = Radiographer
RA=Radiographer Assistant
PHY = MRI Physicist
Blood Glucose (Participant)
Protocol Review and Training (CI)
Participant puts on scrubs
MRI Prep (RG, PHY)
MRI Safety Questionnaire (RA)
OK to proceed?
NO
YES
Thank and prepare to leave MRI Suite (CI, RG, PHY)
Participant Leaves CRC
Initiate sMRI/fMRI protocol (CI, RG,PHY)
OK to proceed?
NO
Complete sMRI/fMRprotocol (CI,RG,PHY)
Thank and prepare to leave MRI Suite (CI, RG, PHY)
Participant Leaves CRC

Appendix T

Participant Training for fMRI

Schedule participant to arrive 45 minutes to an hour before the scan time. Need to get to MRI staff by 20 minutes before the scanning appointment so keep track of the time.

1. Consent Form (Make sure ID # is on top):
   - The document quoted in the first point is the one I sent in mail or email
   - Need to initial every box and sign/date bottom of form to participate
   - Person taking consent sign/date bottom line
   -
2. Blood Glucose
   - Need value 5 or more if below give lucozade or digestives (lucozade if lower than 4) and retest at end of training
   - Record blood glucose value(s)

3. MRI Procedure:

Tell the participant information about what will happen during the exam

a. Radiographer or assistant will go through the questions on the MRI Safety Questionnaire to make sure safe to go in MRI

b. Change into scrubs and put belongings in locker

c. Radiographer and physicist will get you ready on the scanner bed. For the first scan a cage goes around your head with googles so that you can see the thinking tasks on a computer screen. The physicist will adjust the goggles to correct your vision. The machine also makes a very loud noise so you will be given earphones to protect your ears. You won't be able to talk to us while in the scanner so if you want to stop at any time you will have a bulb to squeeze to contact the radiographer. You will be given a trigger to hold in each hand to make responses on the thinking tasks.

d. The first scan will be of your brain that takes a total of 45 minutes. For the first 20 minutes you will have structural scans of your brain to see the different parts. You just keep your head as still as possible – your eyes can be open or closed.

e. The second set of scans, for the next 20 minutes, will be the functional MRI. This shows differences in the activity in your brain when you do a thinking task that is easy and one that is a bit harder. There are two different tasks and one scan to show what your brain is doing while at rest and you will just keep your eyes closed for that one.

f. The third part, for about the last 5 minutes, is a scan of the white matter tracts in your brain that connect one part to another. In this scan you will feel vibrations as if your head is shaking in different directions – this is normal.
g. Next you will get out of the scanner to stretch for a few minutes after this the radiographer will prepare you for the chest scan. This scan takes about 15 minutes. For this scan a cage is put around your chest. You will be given instructions to hold your breath for short periods of time or to breathe normally.

4. fMRI Task Training

For both tasks open the Presentation software on the Dell computer (needs to be plugged in). Go into the Open Experiment tab and choose Nback. When ready to start the scenario, put in the participant ID # when prompted. Then Start Scenario

a. Nback

Verbal instructions: The first task is a memory task called the Nback. You will see one letter presented on the computer screen every second. On the first task, the 0back, you will press the button on the right (L on the keypad) every time you see the letter X, when you see any other letter you will press the button on the left (A on the keypad). This is the easy task. On the second task, the 2 back, you will be asked to press the right button (L) every time you see a letter that is the same as 2 letters before. You press the left button (A) for every other letter. For example (Show example on sheet included with these instructions) if the letters are A, B, C, B, B you would press the left button for A, B, and C then the right button for the next B because you saw a B two letters back, and left for the next B because it is only the same as the letter 1 letter back or 3 letters back, but not 2 letters back. The best way to do this is to repeat the first set of three letters (A, B, C), then update with the next set of 3 letters (B C B) then the next (CBB) and then you can compare the first letter with the third to know if you should press right or left button. I'm going to show you on the computer so that you can try it for yourself.

Make sure you press one of the buttons every time you see a letter. I want you to get as many right as possible, but don't worry if you make a mistake just go on to the next letter – because they keep going. The important thing is to keep focused and try your best on the task because I'm just interested in what your brain is doing when you are doing the easy 0back compared to when you do the harder 2back.

Let the task run through until you are sure the person understands. At first the trainer says the responses out loud while the person presses the button, and once they get the hang of it let them do it on their own and watch the responses to make sure they are getting it right – if not give more instructions as necessary until the person learns the task). For the

2back repeat the letters out loud to show how to update the 3 letters to determine what button to press – if they make mistakes encourage them to just focus on the letter presented and start again from there. Press esc to stop task once participant gets the hang of it. You can run through one more trial if necessary by loading the experiment again and changing the participant ID a bit (add letter a after the number).

b. Inspection Time
Change to the Inspection Time Presentation file

Instructions: On the computer screen you will first see a small cross – this is just a sign to tell you to wait for the next picture. Next you will see two lines attached by a line at the top. One line is twice as long as the other. You have to press the right button (L on the keypad) if the longer line is on the right (*Show the picture with the long line on the right).* You have to press the left button (A on the keypad) if the longer line is on the left *(Show the picture with the long line on the left).* What makes it more difficult is that you will be shown the pictures very quickly and it will show for varying times, less than a second so sometimes it will be harder to see than others. After one of these pictures is shown then the lines are masked out with a forest of other lines to be you can't see it anymore, because even when you take an image out of your view - you may still have an afterimage – like when you look at a lightbulb and can still see it when you turn away – to make sure that this doesn't happen, the lines are masked after you see them with this picture called the forest *(Show the forest picture).* Once you see this picture – the forest - it is a signal that you have been shown one of the two lines and that you should make a response (even if it was too fast for you to see).

On this task it is important to answer correctly. How quickly you answer isn't important, although you need to make a response by the time you see the forest – even if your not 100% sure which one is longer. I will let you try it for yourself until you get the hang of it. (Instruct to press the buttons if necessary).

5. Get ready for MRI
Once training has been done take the participant through to the radiographer/assistant. Remember - need to get to MRI staff by 20 minutes before the scanning appointment

Appendix U

MRI Patient Safety Questionnaire

NHS TAYSIDE
MRI PATIENT SAFETY QUESTIONNAIRE

HEIGHT..... CM
WEIGHT.....KG

PATIENT NAME .....CHI.....

	YES	NO
1. Do you have a pacemaker or other heart implant?.....	☐	☐
2. Do you have an implanted defibrillator for your heart?.....	☐	☐
3. Do you have a replacement heart valve?.....	☐	☐
4. Do you have aneurysm clips or coils in your head?.....	☐	☐
5. Do you have a spinal or deep brain stimulator?.....	☐	☐
6. Do you have any surgical clips in your body?.....	☐	☐
7. Have you had surgery within the last 6 weeks?.....	☐	☐
8. Have you ever had an incident of metal fragments going into the eye?.....	☐	☐
9. Do you wear dentures or a plate with metal in them?.....	☐	☐
10. Do you have any artificial implant, hearing aid or medicated skin patches?.....	☐	☐
11. Do you have any tattoos or piercings?.....	☐	☐
12. Have you removed all jewellery, metal, credit cards, keys, coins, belt etc?.....	☐	☐

It may be necessary to inject a contrast media to outline your anatomy more clearly. The following questions are designed to ensure that this injection can be administered safely.

13. Do you suffer from asthma or are you allergic to anything? If yes, specify.....	☐	☐
14. Have you been admitted to hospital with an allergic reaction.....	☐	☐
15. Do you suffer from any problems with your kidneys?.....	☐	☐
16. Are you pregnant.....Number of weeks.....	☐	☐
17. Are you breastfeeding?.....	☐	☐
18. I agree to additional scans or images being used for training and development purposes.....	☐	☐

THE INFORMATION I HAVE PROVIDED IN THIS QUESTIONNAIRE IS CORRECT

PATIENT SIGNATURE.:.....DATE.....

(Radiographer responsible for scan)
SIGNATURE.....DATE.....