Cognitive Function in Type 2 Diabetes: A Study Using Younger Adults

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LIST OF ABBREVIATIONS

BBB	Blood Brain Barrier
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BMI	Body Mass Index
CVD	Cardiovascular Disease
DAT	Dementia Alzheimer's Type
DKEFS	Delis Kaplan Executive Function System
DM	Diabetes Mellitus
EF	Executive Function
FG	Fasting Glucose
FGT	Fasting Glucose Test
GA	Glycated Albumin
HBA1c	Glycated Haemoglobin
HDL	High Density Lipoproteins
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
K-S	Komogrov-Smirnov
LDL	Low Density Lipoproteins
MI	Myocardial Infarction
MMSE	Mini Mental State Examination
MOCA	Montreal Cognitive Assessment
MS	Muscular Sclerosis
NCD	Non Communicable Diseases
NICE	National Institute for Health and Care Excellence
OGTT	Oral Glucose Tolerance Test
PIS	Patient Information Sheet
PS	Processing Speed
SES	Social Economic Status
SPSS	Statistical Package for the Social Sciences
TOPF	Test of Premorbid Functioning
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus

TG	Triglycerides
VD	Vascular Dementia
VF	Verbal Fluency
WAIS	Wechsler Adult Intelligence Scale
WM	Working Memory
WMS	Wechsler Memory Scale

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ABSTRACT

Background: The rising rates of Type 2 diabetes (T2DM) around the world have serious economic and health implications, often related to the complications of the condition. One such problem is the impact of diabetes on cognitive function. In older adults with T2DM, there is an established relationship between diabetes and cognitive impairment in people with and without dementia. Emerging evidence suggests this may also be the case for younger adults, as the occurrence of cognitive deficits in people with T2DM is related to the severity and duration of the condition. In some parts of the world, T2DM has become the most common diabetes phenotype in children. Therefore, exploring the cognitive function of younger adults with T2DM is important, to understand the pathogenesis and sequelae of the condition across the lifespan.

Aims: To investigate if younger adults with T2DM show signs of cognitive impairment, and how this relates to diabetes-related health indicators.

Method: Ten people with T2DM were recruited from a diabetes clinic in London, and completed a battery of cognitive tests assessing processing speed, attention, executive function, learning and memory. Estimates of optimal (premorbid) ability were also derived. Clinically relevant markers for diabetes were recorded, including Hba1c and lipid profiles.

Results: Scores on cognitive tests suggested deficits in attention and processing speed, but executive function was a relative strength. Scores were not declined relative to one measure of optimal ability across the group. Health markers related to diabetes were correlated with several cognitive domains, although not consistently: total cholesterol levels showed the strongest associations, and not always in the direction anticipated.

Conclusions: Due to the small sample size, any profiles and associations should be treated cautiously. Further research in this area is needed, and cognitive impairment in people with T2DM should be attended to routinely in clinical services.

1. INTRODUCTION, AIMS & JUSTIFICATION

1.1 Literature Search

The search strategy used to inform the literature presented here was undertaken in four stages. The first was a scoping search, by finding existing reviews and becoming familiar with which databases would be included in the final search.

Secondly, key search terms for each database were defined, and further terms were sought using pearl-growing, and this formulated a search strategy.

Third, the database search was performed, using PubMed, PsycInfo, Science Direct, Scopus and Google Scholar, employing free text and thesaurus searching methods (where thesaurus was permitted).

Finally, a bibliography search was conducted by looking at reference lists of papers, key authors and within highly cited or key articles for additional references.

1.2 What is Diabetes?

Diabetes Mellitus (DM) is a metabolic syndrome in humans that is characterised by chronic hyperglycaemia, or high levels of glucose in the blood, that the body is unable to use. In order to use glucose or blood glucose insulin is required, which is a hormone that regulates blood sugar. There are lots of different types of diabetes, but developing the condition is most likely due to one of two reasons: either the body does not produce insulin - Type 1 Diabetes Mellitus (T1DM), or the insulin it produces is ineffective - Type 2 Diabetes Mellitus (T2DM). The ability to regulate glucose in the body is known as glycemic control. Once termed a disease of the West, T2DM is now a global issue and has been called the biggest health epidemic of this century (Tabish, 2007). Whilst it is treatable and accordingly is seen as a long-term condition, every five minutes, someone in the world dies from diabetes-related illness (International Diabetes Federation, 2015).

1.3 History of Diabetes

The symptoms of diabetes were first mentioned in Egyptian manuscripts in 1500 B.C., when it was observed that ants were attracted to the urine of people with an emaciating disease (MacCracken & Hoel, 1997). The condition did not come to have the name 'diabetes' until around 250 B.C. Diabetes, comes from the Greek word for a siphon, as the condition was characterised by liquid leaving the body in the form of excessive urination. The word 'mellitus' (honeyed) was added when a London physician in the late 18th century tasted the urine of his patients with diabetes, and noted that it was sweet (Tatersall, 2010). This was actually a re-discovery as in India 400 B.C., the term 'honeyed urine' was first used. Although the link between diabetes and the pancreas was identified in the 1800s, the connection between diabetes and insulin was discovered later. In 1921, it was established after many years of speculation that an insulin deficiency was implicated in diabetes (Barnett & Krall, 2005).

The subdivision of diabetes into different types was first recognised in the 1700s onwards, noting that leanness (T1DM) or obesity and later onset (T2DM) was commonly associated with the condition (Alberti, 2010). However, the diagnostic terms were established in the mid 60's (World Health Organisation, 1964).

1.4 Different types of diabetes

Although there are several different types of diabetes, for the purpose of the thesis, I will be focusing on explaining the two most common types, T1DM and T2DM, in greater detail.

1.4.1 T1DM

T1DM is an autoimmune disorder that destroys insulin-producing beta cells in the pancreas, and people with the condition can also have insulin resistance (Alberti, 2010). It typically develops in childhood or early adolescence, is normally diagnosed no later than 30 years old and, once diagnosed, people with T1DM require insulin to live. People with T1DM account for about 5-10% of those with a diabetes diagnosis (American Diabetes Association, 2008).

1.4.2 T2DM

Historically, T2DM (referred interchangeably with diabetes from this point on) was known as the older adults' disease. This was due in part to the higher incidence in the older population, estimated as one in four in some countries (Gambert & Pinkstaff, 2006). However, T2DM is now very common in middle-aged adults. It is the most common form of diabetes, with around 90-95% of people with diabetes having T2DM (American Diabetes Association, 2008). It is characterised by either not making enough insulin or the insulin generated being ineffective. Unlike T1DM, people with T2DM do not usually need insulin for survival, but as the condition progresses, people may require insulin to ensure they control their blood sugar effectively (Alberti, 2010).

1.5 Diagnostic Criteria

Typically, people who present with symptoms of diabetes such as thirst, polyuria (excessive urination), weight loss, or recurrent infections would be tested for diabetes. In the last 10 years, there have been three ways in which people around the world have been tested for diabetes by: casual, fasting, and oral glucose load.

1.5.1.1 Casual glucose load: can be measured by a one-off measurement of blood glucose and a definite diagnosis would be given to someone with a blood plasma level greater than 11.1 mmol/L (200mg/dL) or 12.2 mmol/L (220mg/dL) in capillary plasma. Any values between 5.0-11.0 would be uncertain and may constitute 'Prediabetes' or Impaired Glucose Tolerance (IGT) (see below).

1.5.1.2 Fasting glucose test (FGT): is a blood taken after fasting. It is usually done in the morning, as it requires patients not to have eaten or drunk anything for eight to 12 hours before testing. A plasma level of 7.0 mmol/L (126mg/dl and above) may indicate the presence of diabetes. A blood glucose level between 6.1 and 6.9 mmol/L (between 11mg/dl and 125mg/dl) could indicate impaired fasting glucose (IFG).

1.5.1.3 Oral glucose tolerance testing (OGTT): was developed in the 19th century, but only became more common when blood testing became easier to conduct. It was recommended in the first diagnostic criteria defined by the World Health Organisation (1964), who stated that glycosuria – raised sugar in urine - was insufficient to confirm or rule out diabetes. Before the test, patients are asked to eat at least 250g carbohydrates for three days prior to testing, and to refrain from eating or drinking certain fluids, eight to 12 hours before testing. As part of the test, the patient will have their blood tested, then be given a glucose drink, and their blood will be tested again two hours later.

1.5.1.4 'Borderline diabetes' or 'Prediabetes': is a concept that has emerged since the late 1970s, where people without diabetes had blood plasma levels of glucose, which were higher than normal. The World Health Organisation (1980) named this Impaired Glucose Tolerance (IGT). Later, the concept of Impaired Fasting Glucose (IFG) was added, to indicate blood glucose that was high but below the threshold for a diabetes diagnosis. The presence of both IGT and IFT in a person, has led to the introduction of a label known as 'prediabetes', although not everyone affected will go on to develop diabetes. In this sense, the label is seen as less helpful and some relevant bodies prefer the term 'intermediate hypoglycaemia' (World Health Organisation, 1999).

1.5.2 Hba1c

Although raised blood glucose has been a cornerstone in identifying different types of diabetes for over 100 years (Alberti, 2010), it has its problems with its accuracy. Hba1c, also know as glycated haemoglobin, measures glycaemic control over weeks, rather than at a specific moment in time. It gives a better indication than an oral or fasting glucose test that a person is hypoglycaemic, and with better accuracy (Alberti, 2010). However, it is expensive and its validity as a standardised measure was called into question, as there were variations in the methods used in laboratories. Recently, more widespread use of Hba1c as a diagnostic measure of diabetes has been recommended (American Diabetes Association, 2009). The World Health Organisation (2011) also followed suit, with a caveat that when Hba1c is used diagnostically that "there are no conditions present that preclude its measurement" (p.3). The diagnostic criteria for using

Hba1c is a cut off of 6.5% for diagnosing diabetes, but anything below this does not rule out diabetes diagnosed via glucose testing.

1.5.3 Variation in diagnosis around the world

As the implications of diabetes can be lifelong and difficult, it is important that diabetes is diagnosed correctly. However, as mentioned previously, the criteria that has been used for diabetes diagnosis has varied worldwide – in part due to availability of Hba1c testing. As such, when evaluating relevant studies of people with diabetes, the accepted diagnosis will either be using Hba1c or by casual, fasting or oral glucose testing.

1.6 Epidemiology of Diabetes

Using the above diagnostic criteria, in 2015, there were 2.8 million people in the UK and 415 million people worldwide with diabetes. By 2040, that is estimated to rise to 3.5 million people and 642 million respectively (International Diabetes Federation, 2015). Currently, those figures equate to 1 in 11 having diabetes, rising to one in 10 in less than 30 years time. The global cost of diabetes annually is estimated as $825 billion (NCD Risk Factor Collaboration, 2016), with approximately 12% of global health expenditure on diabetes. The healthcare cost of people with diabetes is calculated as around two to three times higher than a person without diabetes (International Diabetes Federation, 2015). The reason for this difference is partially explained by the rising cost of medication, but also the increase in numbers of people with diabetes and diabetic related complications.

1.7 Management of Diabetes

As every person with diabetes is different, the management of the condition is done in various ways. However, in the UK there are several aspects of diabetes care that are standardised. According to the National Institute for Health and Care Excellence (2016b), as someone with T2DM, one should expect the following from your diabetes healthcare professional:

- Advice about local support groups
- The opportunity to attend a diabetes education group
- Diet and lifestyle advice
- An annual blood pressure check
- Regular blood glucose check
- Quarterly to bi-annual Hba1c check
- Discussions about medication to control your blood glucose
- Where necessary, discussions about insulin and how to inject properly
- Explanations about hypoglycaemia or ‘hypos’, and the symptoms, risks and treatment
- Exploring risk of cardiovascular disease now and in the future
- Offering regular eye screening and foot checks
- Checking other possible complications such as kidney disease or nerve problems

As a result, the burden of diabetes is high and this is on several levels: to the individual in terms of health-related burden e.g. medication (Black et al., 2015), social burden – including the impact on the family and retaining gainful employment (Von Korff et al., 2005), and the associated economic impact of diabetes, both directly because of health expenditure and also the indirect cost, due to lack of productivity e.g. being unable to work (Ali, Weber, & Narayan, 2015). As a result of these factors compromising a collective burden, there is interest worldwide to reduce the impact that diabetes has on multiple levels in society.

1.8 Complications of Diabetes

As part of the global health agenda, diabetes is the most common of four non-communicable diseases (NCD) (cannot be transmitted from person to person) that are focused on by world leaders due to the disability and premature death they cause. People with diabetes are at increased risk of developing complications if their blood glucose levels remain high. These complications can make diabetes more difficult to manage but can also cause life altering disabilities or even death. Whilst diabetes care is aimed at making sure that hyperglycaemia is avoided, a secondary aim of diabetes management is preventing damage to the human vascular tree of the body (Fowler, 2008) - including microvascular (small) and macrovascular (large) blood vessels.

1.8.1 Microvascular complications

1.8.1.1 Retinopathy: is an eye disease affecting the blood vessels, which can lead to vision loss or blindness. The cause of retinopathy in diabetes is consistently high blood glucose. Retinopathy can be at an advanced stage before symptoms are detected so regular eye screening is recommended for people with diabetes.

1.8.1.2 Diabetic foot and nerve damage: can develop in people with diabetes because of reduced blood flow to the extremities, which causes nerve damage. The nerve damage occurs due to high blood glucose levels over time. The most common form of nerve damage in diabetes is peripheral neuropathy affecting the feet, but it can also affect other parts of the body such as the hands. The nerve damage causes pain, tingling and numbness, which can be problematic because symptoms in the feet can go undetected for some time, leading to infections, ulcers and sometimes amputation. Other complications from nerve damage include problems with urination, erectile dysfunction, vaginal dryness and loss of sensation, amongst other complaints.

1.8.2 Macrovascular complications

1.8.2.1 Hypertension: is defined as high blood pressure which is considered to comprise a systolic pressure (the force at which your heart pumps blood around your body) of 140 or above and a diastolic pressure (the resistance to the blood flow in the vessels) of 90 or above e.g. 140/90 or higher. It affects between 67% and 71% of people with T2DM (Suh, Kim, Choi, Plauschinat, & Barone, 2009; Centers for Disease Control and Prevention, 2014). As such, hypertension is often seen as a condition that interacts with diabetes, and shares several underlying risk factors, including ethnicity, familial risk and lifestyle (Long & Dagogo-Jack, 2011). Whilst hypertension has been highlighted as a macrovascular complication, like diabetes, it can have implications on a microvascular level as well. Hypertension without diabetes is best managed by blood pressure monitoring, medication and lifestyle changes, such as a healthy diet and regular exercise, and reducing smoking, alcohol, salt and caffeine intake (National Institute for Health and Care Excellence, 2016c). Hypertension that is concurrent with diabetes is managed similarly, but focuses on medication, improved glucose and lipid control (National Institute for Health and Care Excellence, 2016b).

1.8.2.2 Cardiovascular disease (CVD): refers to several conditions affecting the heart such as angina, myocardial infarction (MI or heart attack), congestive heart failure, peripheral artery disease and stroke. These conditions do not develop exclusively as a result of high blood glucose, but are also affected by dyslipidaemia (abnormal levels of lipids in the blood) and hypertension. CVD is the biggest risk factor for people with diabetes and they have a two to four fold risk of developing CVD across their lifetime compared to people without diabetes (Kannel, 1985), with men more likely than women to develop it (Kannel & McGee, 1979). CVD is the leading cause of disability and death of people with diabetes. However, there are a number of factors that can mitigate this risk and research has focused on aspects of how someone comes to develop CVD.

1.8.2.3 Dyslipidemia: is defined as an abnormal level of lipids in the blood. This could be indicated by a high level of low-density lipoprotein cholesterol (LDL) or a

low level of high-density lipoprotein cholesterol (HDL) in the blood. Both LDL and HDL are implicated in the development of CVD as the former seems to be atherogenic (it promotes the formation of fatty deposits in the arteries) while the latter is atheroprotective (it protects from atherosclerosis) where the arteries become blocked by fatty deposits (Viljoen & Wierzbecki, 2010). Dyslipidemia in diabetes is characterised as the pattern of having decreased HDL, increased LDL and triglycerides (TG) (fat in the blood), (Musunuru, 2010), and all three combine to be an independent risk factor of CVD (Manjunath, Rawal, Irani, & Madhu, 2013).

Targets for optimum lipid control in someone with diabetes should be total plasma cholesterol <4.5-mmol/L (~175 mg/dL) and LDL <2.5mmol/L (~100mg/dL), at least. Whilst no targets are set for HDL and TG, HDL concentrations in men <1.2mmol/L (~40mg/dL) and women <1.2mmol/L (~40mg/dL) and TG >1.7mmol/L (~150mg/dL) would be an indication of increased CVD risk (Graham et al., 2007).

1.8.3 Metabolic Syndrome

T2DM is connected with 'metabolic syndrome' – a set of cardiovascular risk factors, including hypertension, hyperinsulinemia (abnormal glucose tolerance), visceral abdominal adiposity, dyslipidaemia, and pro inflammatory states. These risk factors are inextricably linked and once combined in an individual, are sometimes indistinguishable as distinct conditions. Each condition that is present in a person exponentially increases their risk of developing chronic heart disease and mortality (Ali et al., 2015).

1.9 Risk factors in developing diabetes

1.9.1 Obesity and Overweight

One of the most important and modifiable risk factors for developing T2DM is obesity. Obesity accounts for 80-85% of the overall risk for developing diabetes (Huner, 2015). Obesity is defined as an excess of adipose tissue or fat, to the extent that health may be impaired (World Health Organisation, 1999). This excess fat is of most concern when it is distributed in a specific place, such as the

abdomen. This central adiposity is seen as more serious than fat that is distributed more evenly around the body.

In fact, the relationship between diabetes and overweight also indicates that abdominal fat distribution is an independent risk factor for developing diabetes (Ohlson et al., 1985). This is because the presence of excess body fat seems to promote insulin resistance and prevent insulin secretion, or it can produce a pro-inflammatory chemical response that modulates insulin sensitivity (Shoelson, Herrero, & Naaz, 2007). It seems whichever mechanism body fat affects insulin, it is essential in metabolising glucose (Huner, 2015).

1.9.2 Preventing diabetes and its complications

Despite all these conditions being preventable, these complications have become so common that in the USA, only 14% of people with T2DM did not have a comorbid condition (Suh, Choi, Plauschinat, Kwon, & Baron, 2010). Therefore, research has focused on the impact of diabetes, including understanding effective management, treatment and how to intervene earlier to minimise and reduce the complications of the condition (Hu, 2011; Lam & LeRoith, 2012). As mentioned previously, T2DM used to be more commonly associated with older adults. Therefore, much of the research into the pathophysiology i.e. how it affects the body, have focused on diabetes in older populations.

1.10 Older people with Diabetes

Older people are at an increased risk of diabetes as aging is associated with the gradual loss of glycemic control (Resnick, Harris, Brock, & Harris, 2000). Approximately 1 in 4 people who are aged over 65 have diabetes in the United States (Centers for Disease Control and Prevention, 2014). Because of this prevalence, T2DM used to be referred to as the ‘older adults’ disease (Gambert & Pinkstaff, 2006). However, the prevalence of T2DM has been increasing around the world and across the lifespan, and this rise has been linked to higher rates of obesity, sedentary lifestyles and being overweight (Hu, 2011).

The link between aging and developing diabetes is thought to be more complex than originally thought. Research indicates there is a connection between how Alzheimer's Disease (Dementia Alzheimer's Type or DAT) and diabetes both progress in the brain, to the extent that there have been calls to rename DAT 'Type 3 Diabetes' (De la Monte & Wands, 2008). DAT can be considered akin to a metabolic condition, which shares many of the characteristics of diabetes: namely that insulin and IFG resistance and deficiency drive DAT, mimicking the development of diabetes (De la Monte & Tong, 2014). Furthermore, it has long been known that having diabetes is a risk factor for vascular dementia (MacKnight, Rockwood, Awalt, & McDowell, 2002). This would indicate that insulin not only has endocrine implications in the body, but that it has a significant impact on the brain and its functioning (Cholerton, Baker, & Craft, 2013). Therefore, another dimension that should be considered in diabetes is cognitive function.

1.11 Cognitive Function

Cognitive function is a term that refers to the ability to think, remember and process information. In diabetes, one way cognition may be affected is because the functioning of the brain relies on a healthy blood supply. As diabetes is characterised by higher blood glucose, the 'blood quality' may be compromised if the diabetes is not well controlled.

We can measure the extent to which we are functioning cognitively in several ways, but most often this is measured by neuropsychological assessments. There are several domains that can be assessed in neuropsychology, but there are certain areas that are seen as more important to assess in people with conditions such as diabetes.

1.11.1 Processing Speed

Processing speed (PS) refers to our ability to attend to information flexibly and in a timely fashion, using scanning and sequencing visual information. As with attention, processing speed is a construct that can be observed operating on other domains but likewise is an essential skill in cognitive functioning. As

neurons have the highest energy demand and require constant delivery of glucose via the blood, the processing power is determined by this energy supply (Howarth, Gleeson, & Attwell, 2012). Research over the last 15 years into diabetes has shown that in terms of cognitive impairment, processing speed is most typically affected by the presence of T2DM (Stewart & Liolitsa, 1999; Awad, Gagnon, & Messier, 2004; Manschot et al., 2006), although there is some suggestion that vascular complications e.g. heart failure, or smoking status mediate this association (Arvanitakis, Wilson, Li, Aggarwal, & Bennet, 2006).

1.11.2 Attention

Attention is our ability to focus on information, as well as divide and sustain it, often involving mental manipulation and being impervious to distraction from external stimuli. There is no test that measures attention in itself but it is regarded as a building block for other cognitive skills, so it is a necessary thing to measure as a foundation for all cognitive skills (Hebben & Milberg, 2009). Some studies have indicated that attention can be compromised in people with T2DM (Manschot et al., 2006), although other more longitudinal research into the effects of diabetes on attention did not find a direct association between T2DM and attention (Degen, Toro, Schönknecht, Sattler, & Schröder, 2016).

1.11.3 Executive Function

Executive function (EF) is ability to take in information, hold it in mind and do something with it, and it is connected to self-control and regulation. EF also compromises other domains such as inhibition, regulation, working memory and switching between tasks. Meta-analyses assessing the impact of T2DM on EF in older or middle age populations have found EF significantly lower in people with diabetes compared to non-diabetic controls (Vincent & Hall, 2015). This relationship between EF and T2DM has been observed in both Eastern and Western populations that are 65 and older, but also that cognition overall was compromised compared to non-diabetic controls (Zhao et al., 2015).

1.11.4 Memory

Memory refers to our capacity to encode, store and retrieve information and is usually assessed both verbally and visually. Manschot et al. (2006) found that

alongside other cognitive domains, verbal memory was most impacted in people with diabetes compared to non-diabetic controls. A cross-sectional sample of older adults without dementia found that deficits in semantic memory (and processing speed) were also associated with the presence of diabetes (Arvanitakis et al., 2006). However, in other research using a control group, a significant difference was not found for memory once presence of hypertension was controlled for (Van Harten et al., 2007). More recently, research into which memory processes are affected by diabetes has shown that explicit memory (e.g. consciously remembering previous experiences) is most compromised in people with T2DM compared to cognitively normal older adults (Redondo, Beltrán-Brotóns, Reales, & Ballesteros, 2015).

1.12 Factors contributing to Cognitive Function

1.12.1 Premorbid functioning

Usually, information about a person's cognitive function is not available before they develop a condition or an injury. Skills such as vocabulary and word reading correlate highly with general level of ability and are hypothesised to remain intact after an illness develops in some neurological conditions. Therefore, premorbid functioning estimates the optimal ability of someone before the onset of illness (Hebben & Milberg, 2009). In the context of diabetes, very little information is available in the literature about T2DM and premorbid functioning, One study that specified in the title that its focus was premorbid functioning did not use any measures to assess it (Wong, Scholey, & Howe, 2014), and others were small scale samples (N=<40) which found no differences between middle aged and older people with T2DM and a control group (Cosway, Strachan, Dougall, Frier, & Deary, 2001; Asimakopoulou, Hampson, & Morrish, 2002). Therefore, there is very little literature available about optimal ability and people with T2DM.

1.12.2 Mood and Anxiety

For all people with diabetes, it is estimated between 10-30% of those also have depression (Ali, Stone, Peters, Davies, & Khunti, 2006; Adriaanse & Pouwer, 2016). However, age can make a difference, as older adults with diabetes are twice as likely to be depressed compared to those without diabetes (Munshi et al,

2006). Although depression is thought to be more common in people with diabetes (Fisher et al., 2008), having diabetes is associated with the development of other affective disorders, such as anxiety (Kruse, Schmitz, & Thefeld, 2003). Indeed, self-report research of people with diabetes has put the estimated prevalence of anxiety symptoms as double that of the general population (Collins, Corcoran, & Perry, 2009).

Developing mental health problems whilst having diabetes has been linked to the treatment burden of the condition, both psychological and physical, as the treatment regime relies heavily on strict self-management. Experiencing comorbid depression and diabetes is also associated with higher use of health services and entails increased cost (Egede, Zheng, & Simpson, 2002). Furthermore, the relationship between depression and diabetes control is thought to be bi-directional, with one impacting the other in a vicious cycle (Adriaanse & Pouwer, 2016). Despite this understanding, the process of how they come to affect each other in neurological terms is yet to be disentangled.

1.13 Correlates of Cognitive Function in Diabetes

Whilst there is extensive research into how T2DM affects the brain, there are no definitive neurological areas that are always affected by it. This is most likely due to the fact that firstly, the pathophysiology of the condition is still not well understood in this context (Kodl & Seaquist, 2008); and secondly, it may be in part due to T2DM being a syndrome rather than an established set of symptoms that can vary widely from person to person. Therefore, it is useful to summarise what is understood by considering relevant clinical markers in diabetes and their potential relationship to cognition:

1.13.1 Cognition and Hba1c

As noted earlier, Hba1c is seen as the preferred measure of glycemic control. Over a period of nine years, a study of older adults found that higher levels of Hba1c were associated with worse cognitive function and overall decline (Yaffe et al., 2012). In a sample of over 4000 older adults, Zhong, Jin, Xu and Fu (2015)

found that the ratio of Hba1c to Glycated Albumin (GA) was negatively correlated with cognitive function in a non-diabetic population.

Research into memory and diabetes in older adults has found that whilst diabetes can accelerate memory loss, a higher Hba1c in people without diabetes can also predict memory decline (Marden, Mayeda, Tchetgen, Kawachi, & Glymour, 2017). However, despite the large sample size of nearly 9000 older adults, the test of memory selected – the Informant Questionnaire for Cognitive Decline - was not typically used in neuropsychology and therefore, cannot be compared to other tests in a meta analyses, nor directly to Western constructs of tests of memory e.g. Wechsler Memory Scale.

As with much of the research in the area, the conclusions drawn rely on crude means of measuring cognition typically used by psychiatrists, such as the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). Brief screenings for dementia such as the MMSE, are not widely considered as suitable to sensitively measure cognitive defects (Tombaugh & Mcintyre, 1992). It would seem there are some methodological issues with existing research into diabetes that are yet to be addressed.

1.13.2 Cognition and hypertension

As around 2/3 of people with T2DM also have hypertension (Suh et al., 2009), it has not always been easy to establish hypertension as an independent risk factor for cognitive decline. In a systematic review of evidence into hypertension, Van den Berg, Kloppenborg, Kessels, Kappelle, & Biessels (2009), found that high blood pressure was associated with a poorer cognitive performance in seven out of 11 cross-sectional studies and ten out of 13 studies. Interestingly, some studies also found an inverse U-relationship with low and high blood pressure impacting negatively on cognitive performance. According to the review, the domains affected by hypertension in order of most to least were memory, processing speed, attention and visuo-spatial construction. Language was seen as unaffected by hypertension in all studies included.

Although using medication to treat hypertension has been associated with improved cognitive function (Guo et al., 1999), a Cochrane review found that treating people for hypertension does not protect against cognitive impairment or dementia in later life (McGuinness, Todd, Passmore, & Bullock, 2009). Subsequent studies have found that hypertensive medication could be protective against vascular dementia and other types of dementia, other than DAT (Chang-Quan et al., 2011), although they lack the methodological robustness of a Cochrane review. However, the relationship between hypertension and cognitive decline is still not well understood (Liou et al., 2015). This is possibly explained by the variation used in instruments of measurement e.g. parameters of hypertension diagnosis or cognitive assessment tools chosen.

1.13.3 Cognition and cardiovascular risk factors

Cardiovascular risk factors refer to smoking, hypertension, and diabetes, that seem to mediate the development of cardiovascular conditions e.g. CVD, stroke, ischemic heart attack and so on. Over a period of eight years in a community sample, Anstey, Sargent-Cox, Garde, Cherbuin and Butterworth (2014) found that considered collectively, these risk factors were associated with cognitive decline, and specifically with processing speed, which has already been implicated as a domain that may be affected in diabetes.

A recent meta-analysis has used the data from 19 different studies, involving 54,000 participants, and used cardiovascular risk factors to compute an overall composite cardiovascular risk score. This score was highly correlated with lower cognitive test performance and was deemed to be a useful as a predictive measure of cognitive functioning (DeRight, Jorgensen, & Cabral, 2015).

1.13.4 Cognition and High Cholesterol

High cholesterol in middle age has been found to have a deleterious affect on cognitive function in later life (Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005). However, as people get older, the relationship between high levels of cholesterol and cognition is not clear. The majority of research indicates there is no association between cognitive impairment and cholesterol in older people (Kerola, Kettunen, & Nieminen, 2011). Some research has hypothesised that this

lack of relationship between cognition and lipids in older people may be because of existing vascular pathologies in this population (Ancelin et al., 2014). More recently, this lipid-cognition relationship has been explored in Chinese populations, and it was concluded that high cholesterol was associated with faster global cognitive decline in older people (Ma et al., 2017).

1.13.5 Cognition and obesity

Early research had indicated that the relationship between obesity and cognitive decline, particularly dementia, was unclear. There is some evidence to suggest that as with hypertension, a u-shaped association has been found between BMI status and dementia, specifically being underweight or overweight – that both are risk factors for developing dementia (Beydoun, Beydoun, & Wang, 2008). Furthermore, when controlling for other dimensions of metabolic syndrome e.g. impaired fasting glucose, hypertension and dyslipidemia, obesity seems to be an independent risk factor for the development of DAT. Indeed, over a 10-year period examining the connection between metabolic status and BMI, individuals with obesity who were otherwise metabolically healthy showed a similar rate of cognitive decline to their metabolically disturbed counterparts, with an acceleration of cognitive decline associated with increasing BMI (Singh-Manoux et al., 2012). The association between obesity and cognition is also seen in later older age, with waist circumference being positively correlated with poorer cognition in elderly women (West et al., 2016).

In summary, hypertension, dyslipidaemia, obesity and cardiovascular factors all seem to impact on cognitive function, with or without diabetes. On the one hand, these aspects of health seem to mediate the relationship between cognitive functioning and diabetes, but on the other act as independent risk factors for cognitive decline, in their own right. With these existing hypotheses in place, the next consideration is how diabetes can impact the brain at the structural level.

1.14 Diabetes and CNS Neuropathology

1.14.1 Structural Changes

There are certain areas of the brain and structural changes that are typically affected in diabetes. For example, research has found a relationship between diabetes and a reduction in grey matter density, changes in white matter, atrophy, and brain volume loss (Seaquist, 2010; Erus et al., 2015). However, these are general changes that are usually secondary to primary problems, and so making a direct causal link between diabetes and these structural changes is difficult because of the confounding aspects of the comorbid conditions of diabetes. Manschot et al. (2006) found that people with T2DM showed cognitive impairment and structural changes, including increased brain atrophy – e.g. brain wasting, compared to people that did not have diabetes. They hypothesise that these cognitive deficits were related to these structural changes in the brain, most likely due to vascular problems and/or cognitive aging. Later research has also implicated brain atrophy as a mediating factor in developing cognitive impairment in T2DM, rather than cerebrovascular lesions (Moran et al., 2013). Therefore, it is still unclear as to how brain structure interacts with cognition and diabetes.

1.14.2 Glucose

There is still some uncertainty as to where in the brain may be affected by high levels of glucose, and therefore the skills or intelligence that it may impact.
The brain uses about 20% of all sugar energy in the body, despite only accounting for around 2% of body weight (Erbsloh, Bernsmeier, & Hillesheim, 1958): this equates to approximately 5.6mg glucose per 100g brain tissue per minute. As the brain depends on glucose as its main source of energy, the importance of glucose regulation cannot be downplayed: neurons are generally intolerant of any disruption to the energy supply to the brain and diseases can develop as a result (Mergenthaler, Lindauer, Dienel, & Meisel, 2013). However, factors other than physiology may also affect an individual's cognitive function.

1.15 Effects of cognitive decline in managing Diabetes

To effectively manage diabetes, one is required to employ a rigorous self-management program (Peel, Douglas, & Lawton, 2007). A daily regime may include medication, injections, carbohydrate counting, daily blood glucose monitoring, and exercise, although this list is not exhaustive. In order to comprehend why one would need to employ such a regime, requires a basic understanding of the condition. Furthermore, to cope with the multiple components of managing diabetes requires patients to be cognitively intact to a sufficient level. In people that have had the condition a long time, this is even more important because of the complication risks associated with increased duration of illness (Hewitt, Smeeth, Chaturvedi, Bulpitt, & Fletcher, 2011).

1.15.1 Research into the impact of cognitive decline on managing diabetes

The issue of the impact of cognitive impairment on diabetes self-management was highlighted over 15 years ago. Sinclair, Girling, & Bayer (2000) found that in older adults with T2DM who were cognitively impaired, patients employed worse self-management behaviours, needed more professional support and were more likely to have been admitted to hospital in the last 12 months, than those with intact cognition. There is thought to be some variation in the impact of cognitive impairment on daily living for people with diabetes and most of the evidence currently focuses on older adults. In younger adults, cognitive impairment could be linked to severe episodes of hyperglycaemia, but much of the evidence for which domains are affected is variable (Kodl & Seaquist, 2008). Therefore, it is difficult to ascertain what cognitive skill is most compromised by poorly controlled diabetes.

1.15.2 Cognitive domains that matter in diabetes management

Munshi (2017) has highlighted the different cognitive domains that if impaired, could interfere with effective diabetes self-management. For example, any change in memory could mean one forgets to: take medication or inject, monitor your blood glucose, eat food regularly, or attend a diabetes appointment. Any problem in executive function could lead to problems with remembering instructions and/or putting them into practice, trying new suggestions, or the

increased risk of making mistakes when implementing these changes. There could be a similar issue with any problems in processing speed, as this requires ability to attend to information flexibly and within a given time frame, for example, at a clinic appointment. Finally, problems with attention could entail that a patient cannot focus wholly on the instructions they have been given. Whilst Munshi (2017) does not emphasise which of these domains is most important, there is an indication that each domain has implications in managing diabetes effectively. Of concern is that the relationship between cognitive dysfunction and well-controlled diabetes in older adults is bi-directional (Munshi et al. 2006): the more cognitively impaired one is, the worse your glycemic control tends to be, developing into a potential vicious cycle (Ojo & Brooke, 2015). This is one of several factors that may not be currently accounted for in typical diabetes management regimes.

1.16 Intersection of Diabetes, Cognition and Context

Within the epidemiology of diabetes, there has been a focus on individual risk factors and ascribing them to a resulting biological outcome, in a causal link. However, this can overlook some of the more social factors that can lead to the 'fundamental causes' of disease (Link & Phelan, 1995). The term fundamental in this context refers to factors that cannot be eliminated by a healthcare intervention, such as low income or geographical location.

1.16.1 Diabetes and Poverty

A major mediator in pathogenesis of diabetes is poverty. According to research looking at the influence of socioeconomic status of people with T1DM and T2DM, in deprived areas there are more people who have T2DM but not T1DM (Evans, Newton, Ruta, MacDonald, & Morris, 2000). There was also a connection with obesity, where an increase in deprivation was linked to a higher BMI. The impact of SES on healthcare outcomes seems multifaceted, as highlighted by Lutfey and Freese (2005) who looked at the health outcome of two clinics for diabetes care, which differed drastically in socioeconomic terms. They found that the differences in SES status, led to variations in the way the clinics were run on a multitude of levels, leading to poorer health outcomes for those in the lower SES clinic. The higher-SES population understood their condition better and the staff provided

better care continuity with these patients. Yet, disproportionately more resources were given to the higher SES clinic than the lower SES clinic, entailing worse diabetes management for the latter group.

More recently, the Commission on Social Determinants of Health (2008) has highlighted that many health outcomes are socially determined. In order to tackle these issues, they suggest the intervention should be focused not just on the biological risk factors of developing conditions but also at addressing these inequities. In a population study of Latinos in the United States with T2DM, Chaufan, Davis, & Constantino (2011) found that whilst participants were fully aware of what they needed to do to manage their diabetes (e.g. eating healthily, exercise and other diabetes-related treatment), they were prevented by doing so because of their 'poverty trap' and their circumstances were often precarious. Despite their personal efforts in attempting to 'treat' their diabetes, they were unlikely to succeed in their endeavours because of the structural inequities at play in their lives.

1.16.2 Cognition and Poverty

Research has also focused on the ways that being in a low SES group can further perpetuate poverty. One hypothesis proposed by Mani, Mullainathan, Shafir, & Zhao (2013) was that poverty requires a different process of thinking that is distinguishable from people who are affluent. Therefore, the mental resources required to think about financial management leave little capacity to think about anything else. In both laboratory and field tests, the authors supported this claim and emphasised that being poor means having less cognitive capacity, in addition to having a lack of funds. They argue that their conclusion is not about poor people per se but about the people who find themselves in poverty.

Some attempts have also been made to explore the sequelae affected by poverty. The extent to which poverty and aging affects cognition functioning was examined in a large population sample to see if socioeconomic status in later life was associated with cognition. Zhang et al. (2015) found that after controlling for demographic factors such as age, education and gender, poverty was

independently associated with lower processing speed. The authors concluded that improving SES would also improve some domains of cognitive functioning in older adults. Looking across the life span, in a cross sectional study, Latin American children who did not have their basic needs met and those who did, were compared on performance in cognitive tests. It was indicated that those children who were in poverty showed a significantly lower performance in executive function, namely working memory and word fluency, and also attention (Lipina et al., 2013). These environmental factors are important to consider, especially with the increased prevalence of physical health problems as a result of social and structural inequalities.

1.17 Young people with T2DM

Until recently, T1DM was considered the form of diabetes that children and young people were most likely to develop and diagnoses of other phenotypes was quite a rare phenomenon (Constantino et al., 2013). However, an epidemiological study in the last two years found the incidence of T2DM had been underestimated and was now the most common type of diabetes in in young people aged 5-29 in some parts of the world (Ke, Sohal, Qian, Quan, & Khan, 2015).

As in adults, diagnoses of T2DM in young people are typically lifestyle-related. However, there are a number of questions about the pathophysiology in this population, as T2DM in young people is less understood (Adamo & Caprio, 2011). Attempts at estimating the impact of developing T2DM at a younger age have put the average life expectancy of someone as 15 years less compared to someone without diabetes (Rhodes et al., 2012). Furthermore, with the onset of T2DM in adolescence or young adulthood, the severe complications that can develop with the condition e.g. cardiovascular problems, were predicted to occur in a person's 40s. When comparing mortality rates of people with T1DM and T2DM, the mortality was increased nearly two-fold, which was often premature death due to cardiovascular disease. This makes younger onset T2DM the more dangerous of the phenotypes to develop (Constantino et al., 2013). As a result of these mortality rates in young onset T2DM, Public Health England have called for

a nationwide diabetes prevention program as they estimated that over 10% of people under 16 were at risk of developing T2DM (Public Health England, 2015).

One area where there seems to be more evidence regarding is in retinopathy in young onset T2DM. Research in the UK has found that developing T2DM in younger age, e.g. onset under 40, leads to aggressive retinopathy in around 80% of participants after 15 years, irrespective of the age of diagnosis (Song, 2016). Of concern was that this debilitating condition would affect people during their working years and that younger people may be at higher risk of developing other diabetes-related conditions (Pulgaron & Delamater, 2014). In the wider research community, there is an acknowledgement that it will take some time to better understand the pathogenesis and impact on services of younger onset T2DM (Constantino et al., 2013; Wilmot & Idris, 2014).

1.18 Rationale

Understanding diabetes and how it develops is of great importance in the world today, because of the multifaceted impact the condition has on health, economy and society at large. When the onset of T2DM is at a younger age, the comorbid conditions one can develop are thought to have a greater impact, such as aggressive retinopathy. Young people will experience the debilitating effects of these conditions during a period in which they are expected to be most active.

Cognitive impairment is a significant complication of diabetes and there is an established evidence base that it occurs in older adults with diabetes. It was initially hypothesised that this was partially related to how long a person had the condition. However, there is some emerging evidence to suggest that cognitive changes can be observed in the early stages of the condition (Ruis et al., 2009). In 2015, T2DM became the most common phenotype of diabetes in children in some parts of the world (Ke et al., 2015) and as yet, the aetiology of it in this population is unknown. As cognitive impairment can have significant implications for diabetes management (Munshi, 2017), it will be important to investigate if this reduced cognitive functioning is observed in younger populations with T2DM. Diabetes already entails a large treatment burden, and mild cognitive impairment

is likely to complicate people's ability to manage their diabetes, as it does in older adults (Sinclair et al., 2000).

If this relationship is found in younger adults, then cognitively impaired individuals may struggle with the diabetes treatment regime as currently recommended (National Institute for Health and Care Excellence, 2016b). To address this issue in older adults, there are adapted forms of treatment suggested for those affected cognitively (Kirkman et al., 2012) and younger adults could need their care package adapted accordingly. In the instance that no cognitive impairment is observed in working age adults with T2DM, then this could indicate a crucial period in which interventions could 'preserve' cognitive functioning. There have also been suggestions for more routine screening for cognitive impairment in older adults as part of diabetes management (Sinclair et al., 2000; Cukierman, Gerstein, & Williamson, 2005), and this research could contribute toward similar conclusions for younger populations.

Furthermore, there is little in the current literature that discusses or assesses the premorbid functioning of people with diabetes in the context of their cognitive impairment (Xia et al., 2013; Monette, Baird, & Jackson, 2014). Therefore, it would be useful to address this gap by using a measure to test this domain in people with T2DM, to assess its utility.

1.19 Aims and Research Questions:

There is an identified link between T2DM and cognitive impairment in later life and from middle age. However, it is unclear if this link will be observed in younger adults with T2DM, as current literature does not focus on this age range. Therefore, this study aims to investigate the cognitive function of working age adults with T2DM aged 18-55. Using cognitive assessments, the questions I will pose are:

- Do working-age adults with T2DM show reduced cognitive function in scores from a battery of neuropsychological measures, compared to the established norms of cognitive tests?

- As existing literature in the field has tended to neglect the formal assessment of premorbid functioning, do working-age adults with T2DM exhibit reduce cognitive function to their own optimal/premorbid ability level?

- If cognitive impairment is observed, to what extent is this related to health indicators related to diabetes, specifically Hba1c and lipid profile?

- How do other demographic factors e.g. age, duration of condition, interact with T2DM and cognitive function in working age adults?

2. METHODOLOGY

2.1 Epistemology

Epistemology is defined as the study of how we have acquired knowledge and view the world as we do. All types of research attempt to investigate and evaluate aspects of the world. Therefore, in order to conduct research, one has to adopt an epistemological position. Hamlyn (1970) outlines four epistemological positions: correspondence theory – which states a belief is true if it matches reality; coherence theory – a belief is true if it is logical and internally consistent; consensus criterion – something is true if a group of people hold it; and the pragmatist criterion – a belief should be upheld if it is useful. I will outline positions akin to these in more detail:

2.1.1 Positivism

Scientific and quantitative research has tended to adopt a positivist approach that purports the world has properties, which are observable and measurable, via sensory phenomenon. This *empirical* approach – that knowledge is derived from the abstraction of mental states – has led to the assumption that science is objective and free from values (Barker, Pistrang, & Elliott, 2002). This approach has been widely critiqued in social sciences, for obscuring contextual factors, which lead us to generate certain conclusions and privilege types of knowledge over others.

2.1.2 Critical Realism

The critical realist point of view evolved from a correspondence theory perspective and was developed to answer the question of whether society could be studied as nature is (Bhaskhar, 1998). This view assumes the world exists independently of what we think about it, and secondly, our knowledge could be fallible about it, and so we cannot be certain about our conclusions. Whilst elements of this approach are appealing, this approach values knowledge to a greater degree than is necessary and in my view, does not privilege the contingencies of where we have come from enough.

2.1.3 Pragmatism

There is no singular definition of pragmatism (Lipscomb, 2011). However, the type of pragmatism I adopt, views ideas such as 'truth' and 'reality' as normative; therefore, we can never be sure that what we observe and the conclusions we make are not influenced by our values or accurately reflect the world around us (Zaccharadis, Scott, & Barrett, 2010). It also allows research to be conducted using a rigorous methodology, with the 'what works' philosophy (Howe, 1998). This commitment to certain views and practices (rather than knowledge) compliments my own perspective of neuropsychology, and allows me to measure aspects of these beliefs in order to progress.

2.1.4 Neuropsychology

Like positivism, neuropsychology also privileges certain knowledge, specifically examining the relationship between behaviour and brain function. Originating out of single case studies used in medicine, its birth is located back to 1861, when Broca identified an area of the brain associated with a speech difficulty in an individual (Luria, 1973). Whilst these idiographic methods are less favoured nowadays, nomothetic approaches that look at groups of individuals are preferred. However, within a framework of falsification, idiographic or individual cases are still used as counter examples to existing theory in a certain domain. In these instances, having a contextual understanding of these counter examples to existing theory can be essential to understanding 'what works'.

2.1.5 My position

In summary, pragmatists conduct research in relation to their personal value system (Teddlie, 2005). I believe finding out if people with diabetes are being overloaded by their treatment, is of value. Through my clinical work, I have seen how difficult diabetes can be to manage, and how people get treated when they cannot manage their diabetes. I had always wondered whether there was something that was being missed from their care; perhaps understanding people's psychological wellbeing and cognitive state within a different framework would help management of the physical demands of the condition? As such, my connection to research is a *pragmatist* perspective – one's cognitive state exists without us examining it. We may be mistaken in our approach, and we should

use ‘what works’ to investigate it, being mindful this is both a local and Western position and may not be equivalent across all cultures (Van de vijver & Poortinga, 1997; Fernandez & Marcopulos, 2008)

2.2 Design

The study employs a cross-sectional correlation design, which looks at the relationship between cognitive impairment (dependent variable) in a population who has T2DM, and relates it with a number of independent variables: diabetes status (comparing the sample to existing norms), premorbid functioning, diabetes control (Hba1c – continuous) and diabetes-related factors (age, duration of diabetes, education level and lipid profile). In the diabetes context, ‘cognitive function’ alleges four main domains: processing speed, memory, attention and executive function. This design also allows one particular group to be compared to other participants for tests of reliability and difference.

2.2.1 Control group

Initially, there was a plan to include a control group with live-in or home controls e.g. spouse or house mate to do cognitive testing, which would enable comparison to the test population. This would offer a more robust way to examine cognitive performance of people with diabetes in contrast to people without. However, due to a delay in getting ethical approval, this was not practically possible. As such, the decision was made to use the established age-specific norms reported for each test as a comparison. In addition, the population-distributed scores were compared to the putative norms from the subtests in the battery. This approach was taken due to the time and resources available.

2.3 Recruitment

Participants were recruited from one NHS setting that offers integrated diabetes care in the community: the Camden Integrated Practice Unit. A consortium of NHS trusts in the North of London commissions these services. They provide a

multi disciplinary team approach to Diabetes management including nurse specialists, diabetes and endocrinology consultants, podiatrists, dieteticians, and psychologists.

2.3.1 Eligibility Criteria

People with a diagnosis of T2DM can also have several other physical health issues, psychological difficulties and comorbidities. These factors can impact on several areas of functioning, including cognitive capacity. As such, eligibility for the study was informed by existing knowledge from the literature review regarding older adults, T2DM and cognitive impairment.

Whilst inclusion and exclusion criteria were established from the outset, a potential participant's recruitment to the study was decided on an individual basis and was partially informed by the referring clinicians' knowledge of the patients characteristics.

Therefore, the criteria for selection for the study were:

2.3.1.1 T2DM diagnosis: participants were required to have a diagnosis of T2DM. Patients at the unit could have either T1DM or T2DM. In addition, it is not always possible to distinguish between the two phenotypes of diabetes. If there was any ambiguity about this in patients at the recruitment stage, they were not contacted.

2.3.1.2 Demographic information: participants had to be adults aged 18-55, with an understanding of written and spoken English. If patients were able to talk to their referring clinician and follow their written care plan without an interpreter – professional or family member - then they could be tested using the battery of measures.

2.3.1.3 Absence of diabetic complications: significant comorbidities would be prohibitive for participants taking part in the research. For example, one patient had diabetic retinopathy, which is damage to the eye caused by high blood sugars. However, he was being treated and his vision was relatively unaffected.

2.3.1.4 Medical comorbidities: People with diabetes present with a range of difficulties that can arise before or after developing the condition, some of which can affect cognitive functioning. For example, hypertension (high blood pressure) and cardiovascular disease are linked to cognitive impairment (Kilander, Nyman, Boberg, Hansson, & Lithell, 1998; Hassing et al., 2004; Gorelick et al., 2011). There has also been some controversial evidence to suggest that dyslipidemia (high levels of blood fat) is linked to Alzheimer's and other dementias (Reitz, 2013; Moon, 2016), but this was not used to rule people out from recruitment. However, their lipid profile was recorded.

Should participants have comorbidity, their inclusion was considered on an individual basis. For example, if the patient had hypertension, the clinician's view on whether it was well controlled e.g. managing their hypertension within the limits of recommended medical guidance (National Institute for Health and Care Excellence, 2016a) was taken into account before people were recruited.

2.3.1.5 Other conditions associated with cognitive impairment: participants with muscular sclerosis (MS) were not eligible to participate in the study due to the widespread effects it can have on cognition. The areas of functioning that MS tends to effect are information processing, attention, long-term memory and executive function (Chiaravalloti & DeLuca, 2008) – the same areas we anticipated would be impacted in T2DM.

Secondly, we also liaised with clinicians if prospective participants had experienced a stroke, as there is an increased risk of cognitive impairment following one (Gorelick et al., 2011).

2.3.1.6 Mental Wellbeing: In neuropsychological assessment, there is little subcortical specificity for tests administered. Therefore, it is useful to measure emotional wellbeing, to assess whether obtained scores for participants could be explained by an alternative explanation (Hebben & Milberg, 2009). 1 in 5 people with T2DM diabetes also have depression (Ali et al., 2006) and any diagnosis of diabetes is associated with the development of other affective disorders, such as anxiety (Kruse et al., 2003). Developing mental health problems has been linked

to the treatment burden, both psychological and physical, of having diabetes, as the treatment regime relies heavily on strict self-management. On the back of this knowledge, routine questionnaires were given in the clinic to newly referred patients so information about the emotional wellbeing of patients was available. Therefore, any patient who was waiting for psychological assessment from the diabetes psychologist or was currently in treatment was discussed before being offered the chance to participate in research.

People with 'severe mental illness', who had received a diagnosis of bi-polar disorder or schizophrenia were also considered but assessed for possible confounding factors e.g. neuroleptic medication.

2.3.2 Recruitment Process

Using the above criteria, eligible participants were identified by the clinician of the service, by checking the patient information system database of patients who were attending clinic that week. Initially, potential participants were approached in the waiting room. However, this was not successful for two reasons: one, I had no advice from their clinician if they were suitable and two, patients experienced this as stressful.

Therefore, we agreed a record would be kept of which patients were eligible to participate from a clinician's diary, and clinicians would be contacted two days before their appointment to ask 1) would they be suitable and 2) if so, would that patient mind being called about participating in research. If patients said yes to being contacted, participants were offered an information sheet (see Appendix A) at their appointment. This approach was much more successful and all participants were recruited in this manner.

Potential participants were contacted and the study was discussed with them over the phone. Of the people contacted, only two people declined to take part. Those who agreed to participate were offered a date and time to attend the hospital.

2.4 Sample Size

A power calculation was computed for the study in question. If the effect size was 0.8 in a study with two types of predictor e.g. T2DM and cognitive impairment, and, a sample size of 10, a power calculation using G-power indicates a level of 0.32, which is particularly small, indicating just over a 30% chance of detecting an effect if one exists. Whilst this sample size is tied to time and resources, previous studies in this area have adopted similar sized samples. For example, Zhil, Schaaf and Zillmer (2010) who investigated the relationship between neuropsychological profiles of T1DM and T2DM and hypoglycaemic control used a sample size of 12 for their treatment arm for T2DM. Baker et al., 2011 also used similar sample sizes, comparing a group of older adults with high blood sugar (N=11) to those with a diagnosis of diabetes (N=12). In addition, a high statistical power does not necessarily imply credibility of results (Sullivan and Feinn, 2012). However, it is emphasised that the study was exploratory in nature and so results will be interpreted with caution.

2.5 Ethical Issues

2.5.1 Ethical Approval

Ethical approval was obtained from NHS Northumberland Ethics Committee, with provisional approval initially (see Appendix B). Once I had made the agreed changes with an accompanying letter (see Appendix C), I received a favourable opinion (see Appendix D). Following HRA approval (see Appendix E), the Research and Development Department for the Hospital awarded the study access to its patients (see Appendix F).

Ethical approval was also sought from the University of East London ethics committee (see Appendix F). With both of these favourable opinions from the NHS and UEL, I was provided UREC Sponsorship from the university (see Appendix G).

2.5.2 Confidentiality & Anonymity

Record sheets were numbered to maintain anonymity, and the researcher kept a copy of the names of participants separately, which was password-protected, on an encrypted server. Following testing, all tests were scanned and stored digitally, individually password-protected and hard copies were destroyed.

All aspects of testing remained confidential unless there were concerns about a participant's safety or that of others. In the instance where concerns arose, supervisors were contacted, as were other relevant professionals. All of these steps were discussed with the participant before proceeding.

The researcher had access to participants' medical history via their referring clinician and the relevant electronic record (e.g. EMIS), with supervision.

2.5.3 Informed Consent

Participants were given an information sheet (if not already received) to read before signing a consent form (Appendix G). Participants were given an opportunity to ask questions and were encouraged to do so throughout. Testing only began when consent forms were signed. Participants were given the right to withdraw at any time.

2.5.4 Harm Minimisation

A comfort break was offered part way through the session and participants were made aware of this at the beginning of testing. This is to minimise the fatigue that can be experienced when completing neuropsychological tests. Participants were monitored and asked how they were experiencing the tests over the duration of their assessment. At the test completion, participants were asked if they had any concerns about taking part or their performance.

2.6 Procedure

Testing took place in a meeting room or in a clinical room in the hospital. The assessment was completed in one session and took between 60 and 90 minutes to complete.

Initially, demographic information was obtained from participants, including DOB and ethnicity. Next, a short medical history was taken, which included questions about head injury, stroke, MS and kidney problems.

Following this, the battery of neuropsychological tests was administered. The interview protocol was adhered to for each participant (see Appendix J). Once testing was completed, participants were debriefed verbally and given a written debrief sheet including sources of support e.g. Diabetes UK (Appendix K).

Following analysis of their assessment, each participant was sent a written summary of their relative strengths and weaknesses, recommendations for their future care, and an appendices of their scores (should they wish to be or were recommended to be re-tested in the future). As agreed with participants, a copy was sent to their Diabetes clinician. This summary also gave contact details for the researcher and for their relevant professional at the service, should they want to discuss their results.

Relevant medical values regarding their diabetes were also recorded, although this was done via the patient information system with the patient's permission: duration of diabetes, diabetes control e.g. Hba1c and Lipid Profile. A blank copy of the record form is available in the appendices (see Appendix L).

2.7 Materials

The tests chosen were selected for their appropriateness for assessing the constructs that are affected by diabetes: attention, processing speed, memory and executive function. As previously described, much of the literature into cognitive impairment is with older adults. Therefore, tests were selected in concordance with other studies, which assessed processing speed (Stewart & Liolitsa, 1999; Awad et al., 2004), verbal and visual attention (Manschot et al., 2006), executive function (Rucker, McDowd, & Kluding, 2011; Vincent & Hall, 2015) and memory (Arvanitakis et al., 2006; Van Harten et al., 2007; Redondo et al., 2015).

2.7.1 Optimal Ability

It is important to estimate the optimal ability or premorbid functioning in neuropsychology as a baseline by which to measure any form of cognitive impairment (Hebben & Milberg, 2009). In order to do this, the Test of Premorbid Functioning (TOPF) (Wechsler, 2011) was used. This assesses reading ability by presenting the subject with 70 irregularly spelled words, which they are asked to pronounce. The irregular grapheme-to-phoneme require previous knowledge of the word in order to read them, for example, the silent 'b' in plumb. In addition, the TOPF has been validated and co-normed with the Wechsler Adult Intelligence Scale-IV (Wechsler, 2008) and Wechsler Memory Scale-III (Wechsler, 2009). As highlighted in the earlier literature review, this study deemed assessment of optimal ability as equally important as other domains of cognitive functioning, especially as so few studies in the existing literature assessed optimal ability (Cosway et al., 2001).

2.7.2 Verbal Attention

Subtests from the WAIS-IV (Wechsler, 2008) were used to assess verbal attention.

2.7.2.1 WAIS-IV digit span forward: Digit span forward is a measure of verbal short-term stores (STS). It presents numbers orally, in a string of two to nine and asks participants to repeat them immediately back to the examiner.

2.7.2.2 WAIS-IV digit span backward: measures STS plus the ability to manipulate information. A string of two to nine numbers is presented and participants are asked to repeat them back to the examiner in reverse order.

2.7.2.3 WAIS-IV digit span sequencing: measures STS and the ability to control that information. This also requires participants to repeat back orally presented numbers in sequence, from lowest to highest, from a string of two to nine digits in length.

2.7.3 Processing Speed

Subtests from the WAIS-IV (Wechsler, 2008) and Delis-Kaplan Executive Function System (DKEFS) (Delis, Kaplan, & Kramer, 2001) were used to assess processing speed (the ability to do tasks quickly without error).

2.7.3.1 WAIS-IV digit symbol coding: measures the speed in which examinees substitute symbols with a matched key of digits, numbered one to nine, over a two minute period.

2.7.3.2 DKEFS colour word inference – colour word naming: tests how quickly blocks of colour can be named, displayed in red, blue or green. This provides a baseline of a participant's speed of verbal output.

2.7.3.3 DKEFS colour word inference – colour word reading: adapted from the stroop framework, this task assesses how quickly the words red, blue or green, can be read. This gauges speed of verbal output in the participant.

2.7.3.4 DKEFS trail making test – visual scanning: this paper-and-pencil task tests how quickly the number '3' can be identified amongst other digits, numbered one to nine, and cancelled out with a pencil stroke. It provides an estimation of visual-motor scanning speed for the examinee.

2.7.3.5 DKEFS trail making test – number sequencing: measures how quickly numbers one to nine can be identified and connected in sequential order on a page of numbers and letters, 'a' to 'p'. It provides an estimation of visual-motor scanning speed for the examinee.

2.7.3.6 DKEFS trail making test – letter sequencing: tests how quickly letters 'a' to 'p' can be identified and connected in alphabetical order on a page of letters and numbers, one to nine. It provides an estimation of visual-motor scanning speed for the examinee.

2.7.4 Learning and Memory

The Wechsler Memory Scale III (Wechsler, 2009), tests both visual and verbal learning and memory.

2.7.4.1 WMS logical memory: assesses the ability to retain 25 pieces of information based on two stories given, immediately after being presented and with a 20-minute delay. Following delayed recall, participants are asked yes or no questions, which include cues regarding both stories.

2.7.4.2 WMS visual reproduction: measures how well seven designs of increasing complexity that are presented for ten seconds, can be reproduced on paper immediately and with a 20-minute delay. Following delayed recall, participants are presented with six options for each of the seven designs and asked to correctly name the design that was shown.

2.7.5 Executive Function

Three subtests from the Delis-Kaplan Executive Function System (DKEFS) (Delis et al., 2001) were used to assess this domain:

2.7.5.1 DKEFS verbal fluency: timing participants for 60 seconds to assess a) letter fluency –naming as many words beginning with the letter 'F', 'A' or 'S'; b) category fluency – naming as many words that fit the category 'Animals' or 'Boys Names'; c) switching fluency – naming a word from one category, fruit, and then switching and naming a word from a different category, furniture, and alternating for the task duration. It assesses the speed of lexical and semantic speech and output.

2.7.5.2 DKEFS colour word Inference – inhibition and switching: inhibition measures cognitive flexibility by requiring participants to name the colour ink as quickly as possible, whilst the written word is displayed in a discordant colour. The switching task measures the ability to swap between naming the colour ink and naming the ink the word is written in, whilst the word is displayed in a discordant colour. It assesses the capacity to inhibition an irrelevant task.

2.7.5.3 DKEFS trail making test – number letter switching: assesses how quickly letter and numbers can be connected by pencil in sequential and alphabetical order on a page of both numbers and letters e.g. 1-A-2-B. It assesses the capacity to switch between mental sets.

2.7.6 Verbal and Visuo-spatial Functions:

2.7.6.1 WAIS similarities: tests verbal abstraction and requires examinees to describe how two orally presented words are similar (e.g. 'yellow' and 'green', are both colours). The task has 18 word pairs and the task increases with difficulty.

2.7.6.2 WAIS block design: assesses perception and construction by requiring participants to assemble blocks of two, four or nine into a target design. These designs increase in difficulty and are time limited, with more points being awarded the quicker the task is completed.

2.7.7 Mood

2.7.7.1 Beck anxiety inventory (BAI) (Beck & Steer, 1993): is a 21-item self-report measure that includes common symptoms of anxiety. Responders state how much they have been bothered by symptoms in the last week on a four-point scale: not at all, mildly, moderately, and extremely.

2.7.7.2 Beck depression inventory (BDI) (Beck, Steer, & Brown, 1996): is a self-report measure compiled of 21 items of common symptoms of depression. The severity that the responder has experienced each symptom over the last two weeks is indicated by choosing the statement that most applies to them.

2.8 Analysis

The 'raw' scores obtained were converted into scaled scores (Mean =10, SD=3). A copy of the conversion table from scaled scores to labels is available in Appendix M. These scores were inputted into the Statistical Package for Social Sciences (SPSS), version 23. Analyses were performed in accordance with the

parameters of the data e.g. small sample size, which is explained further in the results section.

If the effect size was 0.15 in a study with two types of predictor e.g. T2DM and gender, and the number of predictors was four e.g. age, years of education, duration of condition, a sample size of 11, a power calculation using G-Power indicates a level of 0.60. Whilst this sample size is tied to time and resources, previous studies in this area have adopted similar sized samples (Zhil et al., 2010; Baker et al., 2011).

2.9 Participant Characteristics

In total, 10 participants with T2DM were recruited and completed testing. The characteristics of participants are detailed in Table 1. The participants aged between 34 and 55, with a mean age of 44.9 (Standard Deviation [SD]: 9.19).

Table 1

Descriptive Statistics for Participant Characteristics.

	Mean	SD	Min	Max	Skewness	Kurtosis	Shapiro-Wik Sig
Age (Years)	44.90	9.20	30	55	-.747	-1.094	.089
Education (Years)	13.8	2.57	10	17	-.080	-1.326	.896
Duration	72.90	66.90	8	180	.596	-1.332	.065
Hba1c	76.15	21.30	38.8	106.0	-.151	-.723	.725
Total Cholesterol	4.05	1.01	2.2	5.6	-.005	.418	.599
HDL	1.08	.33	.7	1.7	.824	-.004	.171
LDL	2.00	.88	.6	3.6	.342	.368	.910
Triglycerides	2.15	1.21	.7	4.8	**1.161**	1.341	.189
Beck Depression	16.10	12.22	0	36	.109	-1.296	.495
Beck Anxiety	15.00	13.11	0	34	.423	-1.453	.184

2.9.1 Sex of Participants

Of the sample, six were women and four were men. A chi square test was performed and identified that there was no sex bias, X^2 (1, N=10)= .400, exact sig. = .527.

2.9.2 Birth Country and Language

The sample consists of people who were not born in the UK, and some who had English as a second or additional language. There were six participants who spoke English as a first language and were born in the UK. Participants spoke English as an additional language (Romanian = 1), as a second language, (Ethiopian = 1), as a third language (Lebanese = 1), or were born in the UK and spoke English as a third or fourth language (British Pakistani = 1).

As neuropsychological tests are normed on people who speak English as a first language, it was important to examine if there were any differences in performance in the tests that were administered with participants. A Mann-Whitney U test did not find any significant differences in the scores on the cognitive tests between those who spoke English as a first language and those who did not. This would indicate that language did not significantly impact the performance of the study participants.

2.9.3 Employment status

From the sample, five people were looking for work and five were employed in some capacity, which captures a social inequality in the group.

2.9.4 Comorbidities

With a diagnosis of T2DM, you are at risk from several other conditions that can interact with and complicate the pathogenesis of T2DM. Some participants had CVD (N=1), Hypertension (N=2) that was being controlled with medication and Retinopathy (N=1), which was also being treated. Conditions of this nature would be expected in a population of people with T2DM.

2.9.5 Diabetes-related health indicators

All participants have been diagnosed diabetes, which is a pre-requisite for attending the clinic. They were also required to get their blood tested for clinically relevant markers (e.g. Hba1c, Lipid profile).

2.9.5.1 Hba1c: was obtained from medical notes with participant's permission and this was recorded for all study participants. People with T2DM are advised to

set individual targets with their healthcare professionals about what level Hba1c they should maintain. But as a guideline, patients are advised to keep blood sugars below 48mmol/mol (National Institute for Health and Care Excellence, 2016b). Of the study participants, one person had their blood glucose below this level. Therefore, of the study sample, the majority of people did not have 'optimal control' of their T2DM.

2.9.5.2 Lipid profile: this comprises four figures: total cholesterol, HDL, LDL and TG. This was also obtained for all participants. For one participant, a partial lipid profile was collected due to problems with the blood test at the time.
Targets for optimum lipid control in someone with diabetes should be total plasma cholesterol <4.5-mmol/L (~175 mg/dL) and LDL <2.5mmol/L (~100mg/dL), at least. Whilst no targets are set for HDL and TG, HDL concentrations in men <1.2mmol/L (~40mg/dL) and women <1.2mmol/L (~40mg/dL) and TG >1.7mmol/L (~150mg/dL) would be an indication of increased CVD risk (Graham et al., 2007).

Of the study participants, eight had levels of total cholesterol that were optimum, nine had optimum LDL, and three people in the sample were at increased risk of CVD, based on the concentration of their HDL and TG levels.

2.9.5.3 Duration of diabetes: was recorded in months for all study participants. This is related to existing research that suggests the longer that someone has had diabetes, the more likely they will show complications of the condition.

2.9.6 Cognition related health indicators

2.9.6.1 Head injury: Of the study population, two people had suffered a head injury in the past, and both had received treatment for this. Due to the low numbers in the study population, no further analysis was performed to compare these two participants for any differentiating factors from the rest of the sample.

No one in the population sample had a history of severe mental illness, epilepsy or muscular sclerosis.

3. RESULTS

3.1 Exploratory Data Analysis

For the sample, descriptive statistics were used to look at the mean, SD and data distribution of the demographic, T2DM and age-scaled scores for the cognitive tests. The domains examined were optimal ability, verbal attention, processing speed, executive function, verbal and visual immediate and recall memory, and verbal and visuo-spatial. In addition, the data was scrutinised for skewness, kurtosis and the Shapiro-Wilk statistic was used to see if the data satisfied the conditions for parametric normality.

Skewness shows shape and should be less than 1; kurtosis indicates the peakness and should be no greater than 3, and a significant Shapiro-Wilk ($p<.05$) would indicate the data does not have a normal curve (Field, 2013). The exploration of data showed that most of the demographic variables in the study were mostly normally distributed, as indicated in Table 1. However, participant test scores were not normally distributed and there were a small number of participants. This would indicate that the data does not satisfy assumptions for linear statistics and non-parametric tests should be used.

3.2 Analysis of Cognitive Function

As neuropsychological tests measure performance in areas that change with age, scaled scores were used, which are age adjusted. Descriptive statistics were carried out, and the sample was compared to the putative norm by using a Komogrov-Smirnov (K-S) test. This test looks at how much sampled scores vary from normally distributed scores with the same mean and SD (Field, 2013). If results are significant, we may conclude that the distribution in the sample is significantly different from a normal distribution. This compared the performance of participants on cognitive tests to normative data (M=10, SD=3), which applies to subtests taken from the TOPF, WAIS, WMS and DKEFS.

Visual inspection of the data in Table 2 shows that from the study sample, there are no obvious outliers or areas of difficulty and most data is distributed about the mean. The lowest scores seem to be for Number-Letter Switching and highest for switching output and accuracy.

Table 2

Descriptive and Distribution Statistics for Participants' Test Scores

Subtests (SS)	Mean	SD	Min	Max	Skewness	Kurtosis	Shapiro-Wilk
Optimal Ability	9.40	2.503	4	12	**-1.048**	1.335	.127
Verbal Attention							
Digits Forward	9.40	5.125	3	18	.726	-.797	.129
Digits Backward	8.80	3.155	6	16	**1.529**	2.155	.036
Digits Sequencing	9.00	2.055	5	11	**-1.057**	.386	**.040**
Digits Span	8.50	3.837	4	16	**1.040**	.411	.168
Processing Speed							
Colour Naming	8.20	2.573	4	12	.213	-.513	.574
Colour Word	9.20	3.048	3	14	-.708	1.092	.600
Visual Scanning	9.60	2.171	7	13	.319	-1.343	.321
Number Sequencing	8.00	4.295	2	13	-.042	-1.862	.128
Letter Sequencing	9.20	3.795	2	14	-.727	-.218	.573
Digit Symbol Coding	8.50	2.415	6	13	.917	-.147	.091
Executive Function							
Letter Fluency	9.90	5.065	3	19	.535	-.588	.663
Category Fluency	11.80	4.756	6	18	-.077	-1.929	.143
Switch Output	12.30	4.877	3	18	-.622	-.335	.308
Switch Accuracy	12.70	3.945	5	17	-.793	-.088	.251
Inhibition Scaled	9.80	3.084	5	14	-.505	-.681	.481
Inhibition Switching	8.50	4.197	1	13	-.879	-.163	.159
Number Letter	7.20	4.104	1	12	-.432	-1.598	.187
Learning & Memory - Verbal/Visual							
Story Immediate	10.40	1.897	8	14	.498	-.104	.573
Story Delayed	9.70	2.003	6	13	-.523	.614	.351
Visual Immediate	9.30	3.653	3	14	-.522	-.927	.577
Visual Delayed	10.40	2.951	6	16	.320	.198	.912
Verbal & Visuo-Spatial							
Similarities	8.70	3.020	2	11	**-1.486**	1.475	**.004**
Block Design	8.50	2.369	6	12	.251	-1.839	.086

From the inferential statistics in Table 3, there seems to be a similar pattern: Switching Output and Accuracy (Executive Function) is a relative strength within the population sample, whereas Digit Span and Digit Symbol Coding (Attention and Processing Speed) were relative weakness across the studied sample.

This pattern of relative weakness is partly in keeping with existing research in the area, which suggests that processing speed and attending to information may be impacted (Manschot et al., 2006). However, the pattern of relative strengths for EF is not something we would predict in a sample of people with T2DM (Vincent & Hall, 2015).

Table 3

Participant data for Neuropsychological Tests compared to Normative Data

Subtests SS	Mean of SS of Test	SD of SS of Test	Kolmogrov Smirnoff Z	p
Optimal Ability	100	15	.798	.547
Verbal Attention				
Digits Forward	10	3	1.293	.071
Digits Backward	10	3	1.099	.179
Digits Sequencing	10	3	1.168	.130
Digits Span	10	3	1.362	**.049**
Processing Speed				
Colour Naming	10	3	1.099	.179
Colour Word	10	3	.852	.462
Visual Scanning	10	3	.632	.819
Number Sequencing	10	3	1.293	.071
Letter Sequencing	10	3	.660	.776
Digit Symbol Coding	10	3	1.362	**.049**
Executive Function				
Letter Fluency	10	3	.798	.548
Category Fluency	10	3	1.293	.071
Switch Output	10	3	1.415	**.036**
Switch Accuracy	10	3	1.712	**.006**
Inhibition Scaled	10	3	.481	.975
Inhibition Switching	10	3	.632	.819
Number Letter	10	3	1.14	.167
Learning & Memory - Verbal/Visual				
Story Immediate	10	3	.798	.547
Story Delayed	10	3	.852	.462
Visual Immediate	10	3	.660	.776
Visual Delayed	10	3	.632	.819
Verbal & Visuo-Spatial				
Similarities	10	3	1.168	.130
Block Design	10	3	1.079	.194

3.3 Analysis of Contrast to Estimate of Premorbid Functioning

Tests of premorbid functioning are used to estimate examinee's optimal ability prior to the onset of illness. From the literature review, there was a dearth of research that applied this method. As such, we wanted to explore the relationship between cognitive tests and estimates of premorbid functioning using the TOPF (see Table 4). By comparing the performance on the TOPF to participant's current scores of cognitive tests, we estimate decline in areas of cognitive functioning.

From visual inspection of the data in Table 4, it would indicate from the mean scaled scores that the participants have not shown a significant change or 'impairment' (Means=>3) for any test. Interestingly, there is an improvement in switch accuracy scaled score compared to the TOPF scaled score (M=-3.30) that would indicate an improvement in optimal ability, which is not the direction of the relationship that would be expected. As this was the only variable to show significant change, no further analyses were carried out comparing the TOPF to other tests.

Table 4

TOPF Compared to Other Scaled Scores from Neuropsychological Tests.

TOPF minus SS	Mean	SD	Min	Max	Skewness	Kurtosis
Digit Span Forwards	.00	4.944	-7	6	-.124	-1.761
Digit Span Backwards	.60	2.503	-4	3	-.759	-.746
Digit Span Sequencing	.40	2.011	-4	3	-.893	1.939
Digit Span Overall	.90	3.247	-4	4	-.619	-1.316
Colour Naming	1.20	3.490	-3	8	1.007	.260
Word Reading	.20	2.658	-2	6	1.285	1.297
Visual Scanning	-.20	3.521	-6	5	-.270	-.448
Number Sequencing	1.40	4.671	-6	10	.337	-.073
Letter Sequencing	.20	4.050	-4	10	1.751	3.583
Digit Symbol Coding	.90	2.961	-5	5	-.745	.314
Letter Fluency	-.50	4.116	-9	6	-.544	1.365
Category Fluency	-2.40	3.950	-7	3	.075	-1.896
Switch Output	-2.90	4.864	-11	6	.170	.154
Switch Accuracy	**-3.30**	4.001	-10	4	.158	.155
Inhibition Scaled	-.40	2.836	-5	4	.326	-.110
Inhibition Switching	.90	3.635	-6	7	-.351	.662
Number Letter	2.20	3.521	-2	8	.423	-.912
Story Immediate	-1.00	3.399	-6	4	-.255	-1.188
Story Delayed	-.30	3.592	-6	5	-.486	-.306
Visual Immediate	.10	3.665	-4	7	1.170	.373
Visual Delayed	-1.00	3.055	-6	4	.088	-.551
Similarities	.70	1.636	-2	3	-.350	-1.093
Block Design	.90	2.807	-5	5	-.890	1.309

3.4 Relationship between Diabetes-Related Health Indicators

Due to the small sample size, non-parametric tests were used to look at the correlation between different diabetes-related health indicators: duration of diabetes, hba1c and lipid profile (total cholesterol, HDL, LDL and TG). There were no correlating variables apart from TG and HDL (r=-.795, p<.01).

3.5 Relationship between diabetes markers and cognitive function

Non-parametric tests were also used to look at the correlation between cognitive function (as measured by the scaled scores on the tests) and diabetes clinical information: Hba1c, lipid profile, duration of diabetes. A Spearman's-Rho correlation was selected to explore the relationship and relevant statistics are detailed below.

3.5.1 Hba1c

Hba1c was correlated with a subtest from the learning and memory domain in a visual task, Visual Immediate (r=-.738, p<.01) and verbal-spatial, Similarities (r=-.623, p<.05).

3.5.2 Lipid profile

3.5.2.1 Total cholesterol (chol): was correlated with several variables: verbal attention, specifically Digit Span Forward (r=.746, p<.01), Digit Span Sequencing (r=.558, p<.05) and Digit Span (r=.603, p<.05) subtests; executive function, specifically Switch Output (r=.630, p<.05), Switch Accuracy (r=.674, p<.05), Inhibition (r=.650, p<.05), Inhibition Switching (r=.650, p<.05) and Number Letter Switching (r=.624, p<.05) subtests; verbal learning and memory, Visual Immediate (r=.554, p<.05) subtests; and visuo-spatial construction (r=.724, p<.01).

3.5.2.2 HDL: was correlated with processing speed in the subtest Word Reading (r=-.745, p<.01).

3.5.2.3 LDL: was correlated with EF, specifically the Inhibition subtest (r=.646, p<.05).

3.5.2.4 TG: was correlated with processing speed, in the subtest Number Sequencing (r=-.583, p<.05).

Overall, the Spearman's-Rho indicated a possible relationship between health outcomes related to diabetes and cognitive function, although this is exploratory in nature and should be interpreted with caution.

3.6 Summary of relationship between diabetes clinical markers and cognitive function

With regards to biological markers in the sample, there appeared to be relationships between different factors related to diabetes: Hba1c was negatively correlated with learning and memory, and verbal-spatial tasks, where the higher the Hba1c level was, the lower the performance on the tasks; total cholesterol was positively correlated with tests in all domains apart from processing speed, with a higher cholesterol level being associated with a higher score on some subtests; as HDL and TG affect and are affected by levels of cholesterol in the blood, they were also negatively correlated with tests that measure processing speed. Whilst LDL was significantly correlated with Inhibition, the reason for this is unclear but it is noted there was data missing for one participant for this value, which may have adversely affected the correlation.

3.7 Case Series Analysis

The sample of participants differed across many variables, such as level of education, first language and duration of the condition. As a result, the individual profiles of participants were examined to explore any patterns in individuals, taking into account demographic factors and any concurrent conditions.

3.7.1 Participant One

Participant one was a 32-year old female who was currently unemployed but educated to degree level. She was originally from Romania and spoke English as an additional language. She was diagnosed with diabetes and hypertension in March 2016; her Hba1c was 61% mmol, Lipid: Total cholesterol (chol) 3.9% mmol; HDL 0.7% mmol; LDL 2% mmol; and TG 2.7% mmol.

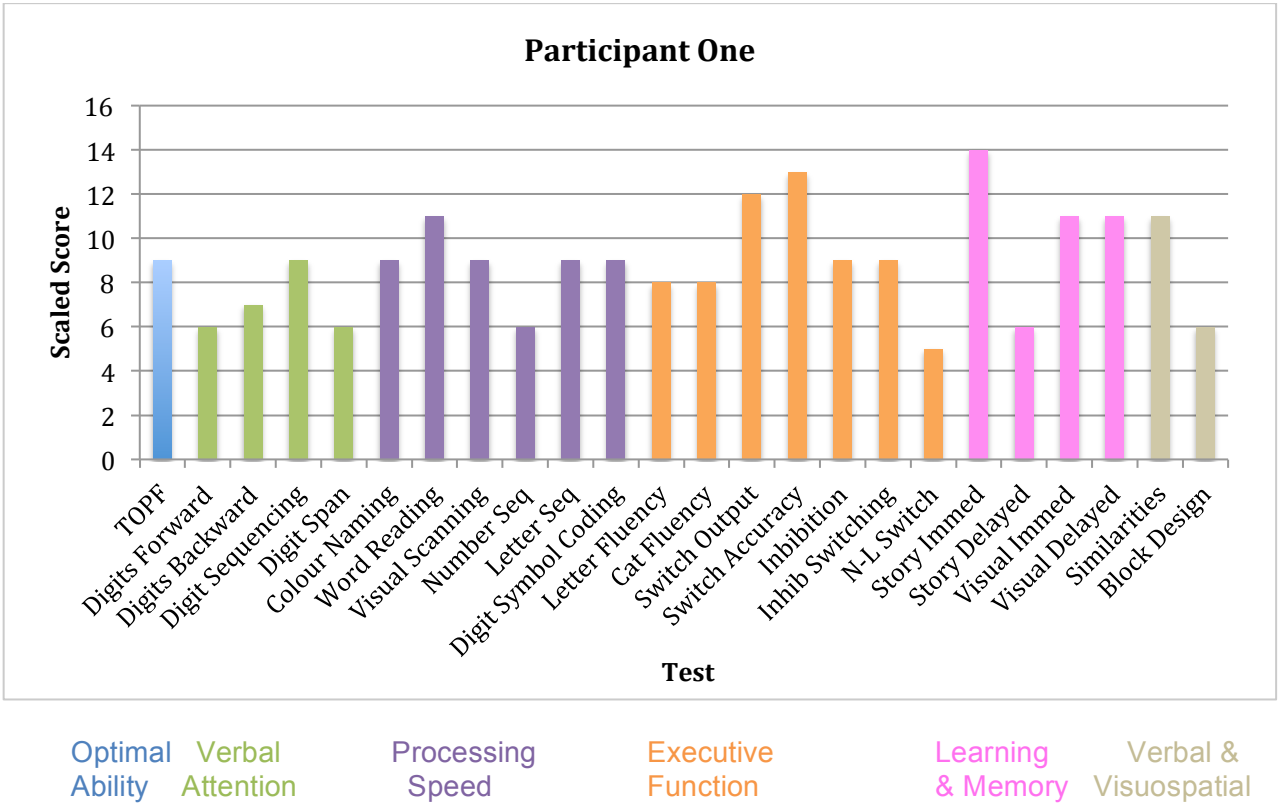

Figure 1. Scaled test scores for participant one.

As indicated in Figure 1, the participant showed relative strength in the domains of Executive Function (EF), specifically Switch Output and Accuracy and Learning & Memory, specifically Story Immediate. There were some relative weaknesses in several domains: in EF there were particular weaknesses in Number-Letter Switching; in Learning & Memory, there was a substantial change between scores of Story Delayed and Immediate; and finally, there were low scores in Block Design in the domain of visuo-spatial construction. Most scores were distributed around the Average-Low Average range, and no scores were categorised as 'impaired'. Her Optimal Ability score did not hold much power as a

predictor of the rest of her scores. Whilst this participant spoke English as an additional language, as she has studied to undergraduate level, it is unlikely to have negatively impacted her performance on this test of reading ability. This participant was being treated for low mood in the clinic, which may partially account for the variability in her scores due to possible psycho-motor slowing in tasks that require attention and mental manipulation.

3.7.2 Participant Two

Participant two was a 51-year-old male who was self-employed and identified as British Indian. He spoke English as a first and only language. He had been diagnosed with diabetes in December 2015 and had some ulceration in his feet for which he was seeing a podiatrist at the clinic. He was managing his diabetes with diet and exercise, and took no diabetic medication. His most recent Hba1C was 89.1% mmol/ml and Lipid: Chol 4.4% mmol; HDL 0.7% mmol; LDL 2% mmol; and TG 2.7% mmol.

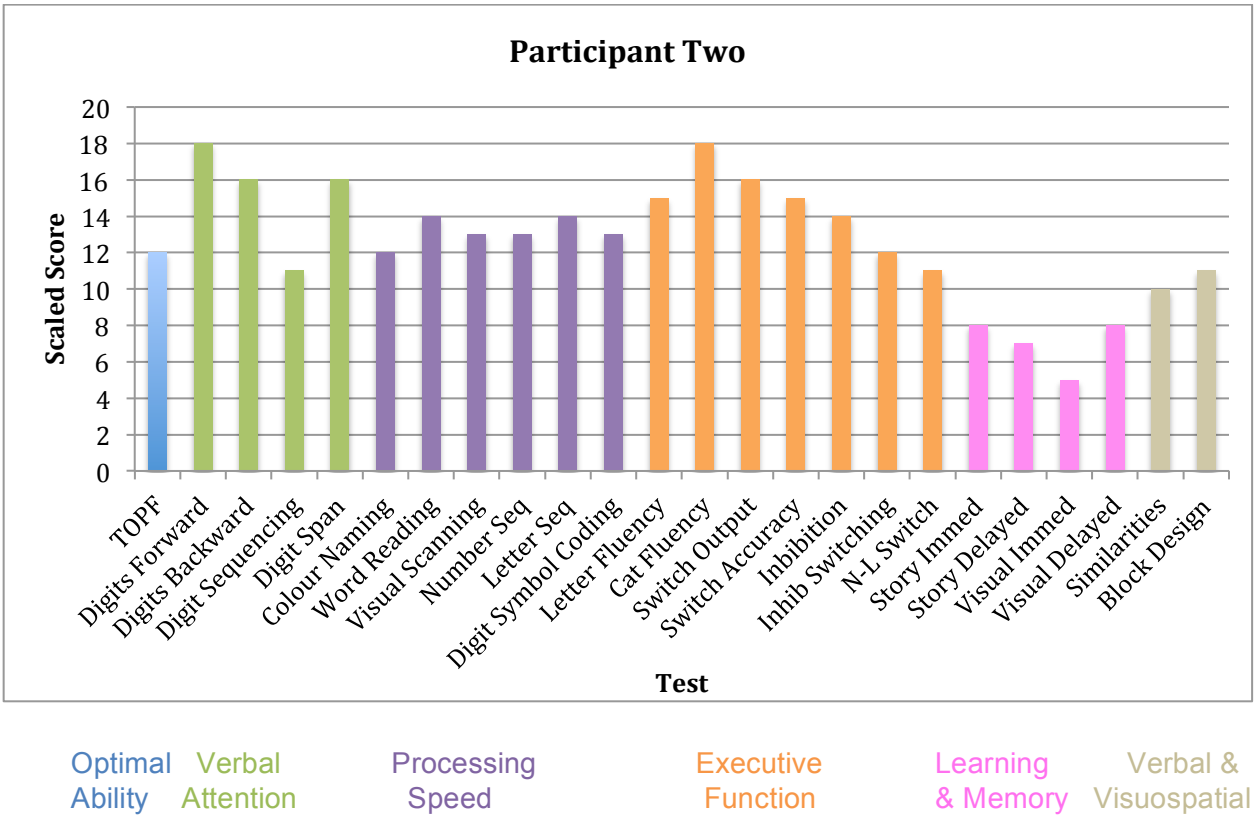

Figure 2. Scaled test scores for participant two.

As seen in Figure 2, the participant showed a strong profile overall, with relative strengths in verbal attention, specifically the Digits Forward subtest and EF, specifically the Category Fluency subtest. There were relative weaknesses in this participants profile in the learning and memory domain, specifically the Visual Immediate subtest but otherwise, most of his skills were intact. The TOPF did not seem to be a good indicator of his optimal ability relative to the rest of his scores.

3.7.3 Participant Three

Participant number three was a 49-year-old Lebanese lady, who spoke English as a third language after Arabic and French. She was not working and was educated to college level. She had been diagnosed with diabetes in 2003: her Hba1c was 101% and Lipid profile: Chol 5.5% mmol; HDL 1.0% mmol; and TG 4.8% mmol. It was not possible to get LDL levels because of a problem with the most recent blood test.

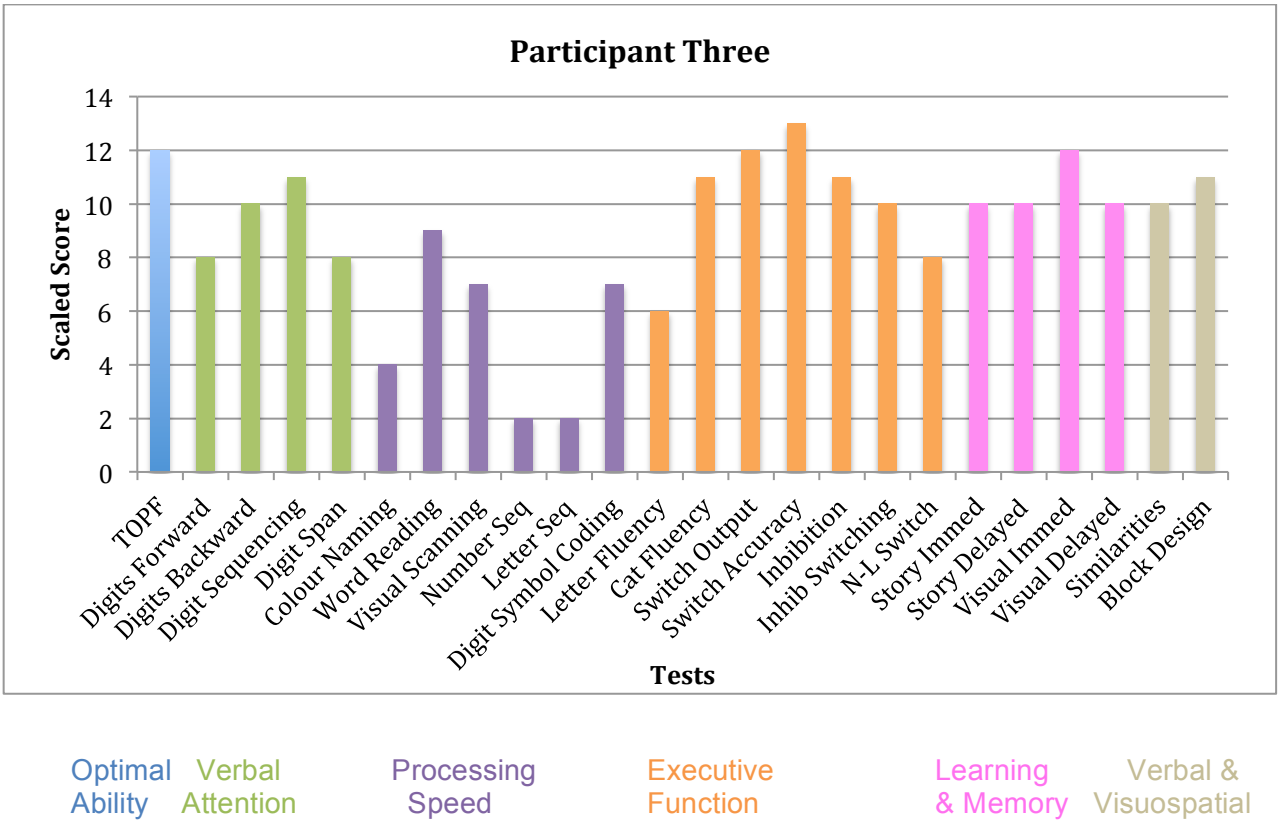

Figure 3. Scaled test scores for participant three.

Figure 3 shows that this participants profile was mixed overall, and most of her scores were in the Average range. There were some relative strengths in EF, specifically the Switch Accuracy subtest and some relative weaknesses and potential decline in processing speed, specifically the Number Sequencing and Letter Sequencing tests. Processing speed is an area that might typically be affected in people with diabetes, and compared to other domains that were tested

it is the most impaired. This profile shows us that this participant's optimal ability is a useful score to measure against her performance across the rest of the tests.

3.7.4 Participant Four

Participant four was a 58-year-old man from Ethiopia, who spoke English as a second language. He was trained as an electrician but was between jobs at the time of testing. He had suffered a severe head trauma in 2001 and was hospitalised for two weeks for treatment. Participant four was diagnosed with diabetes in 2008: his Hba1c was 60.7% mmol and Lipid profile: Chol 3.6% mmol; HDL 0.7% mmol; LDL 1.5% mmol; and TG 3.1% mmol.

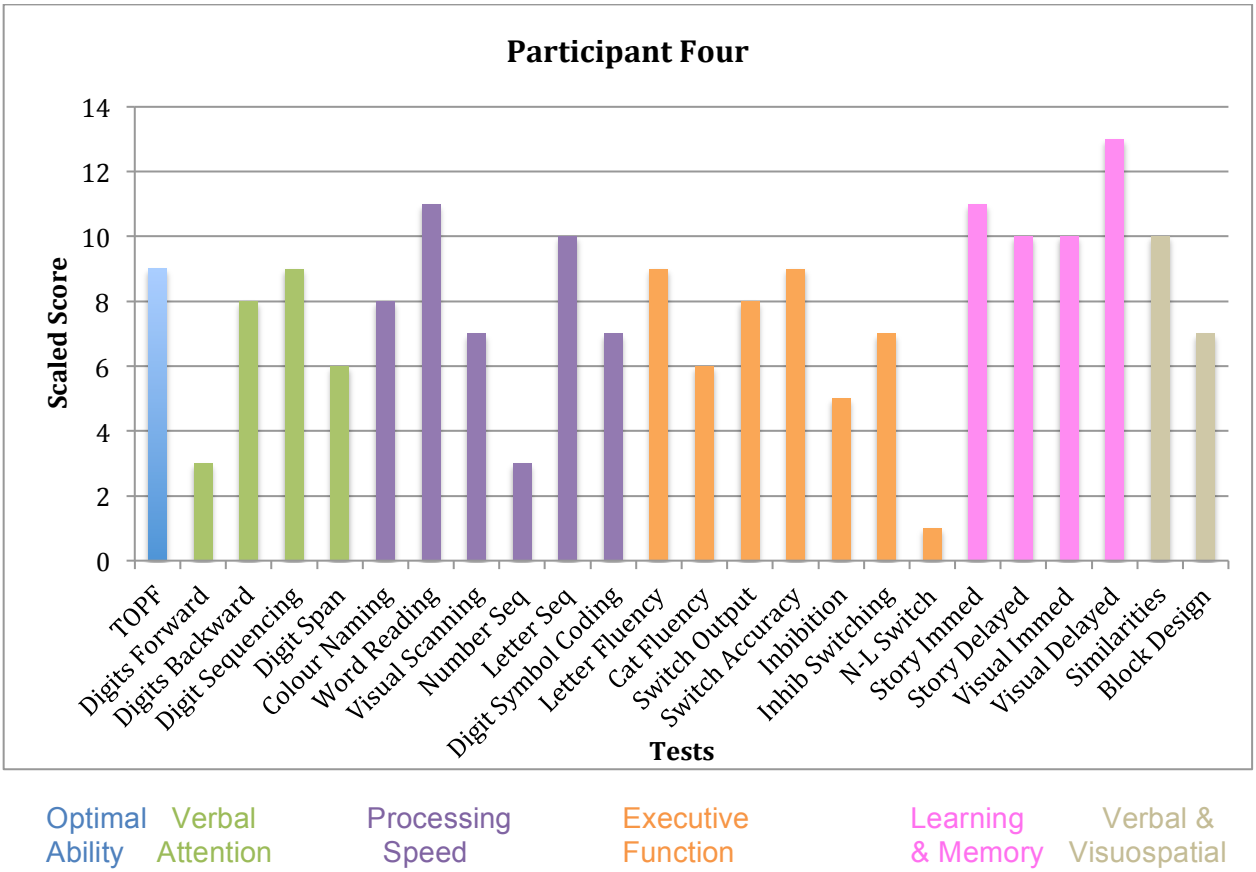

Figure 4. Scaled test scores for participant four.

As seen in Figure 4, this participant's scores were also quite varied. There are relative strengths in learning and memory, specifically Story Immediate and Visual Delayed and some aspects of processing speed on the Word Reading subtest. However, there were also some relative weaknesses and possible decline in processing speed from the Number Sequencing test and also in executive function, Number Letter Switching. In addition, for the tests of verbal attention, it is unusual for someone to get a lower scaled score for Digits Forward

compared to Digits Backward or Sequencing. This discrepancy was attributed to a better understanding of the test rubric later on. The profile for participant four shows us that their optimal ability is a useful score to measure against his performance across most of the tests. Considering that he spoken English as a second language, the impairment seen in some of the performances was interesting: although this was interpreted as a misunderstanding of the tasks, it was recommended that if doing several tasks at once, or holding things in mind became more difficult for participant four, that the cognitive assessment be repeated via the GP.

3.7.5 Participant Five

Participant five was a 30-year-old British female graduate. She was unemployed at the time of testing. Participant 5 had experienced a subcortical haemorrhage, which had been treated successfully. She had been diagnosed with diabetes in 2014. Her Hba1c was 76% mmol and Lipid profile: Chol 5.6% mmol; HDL 1.5% mmol; LDL 3.6% mmol; and TG 1.3% mmol.

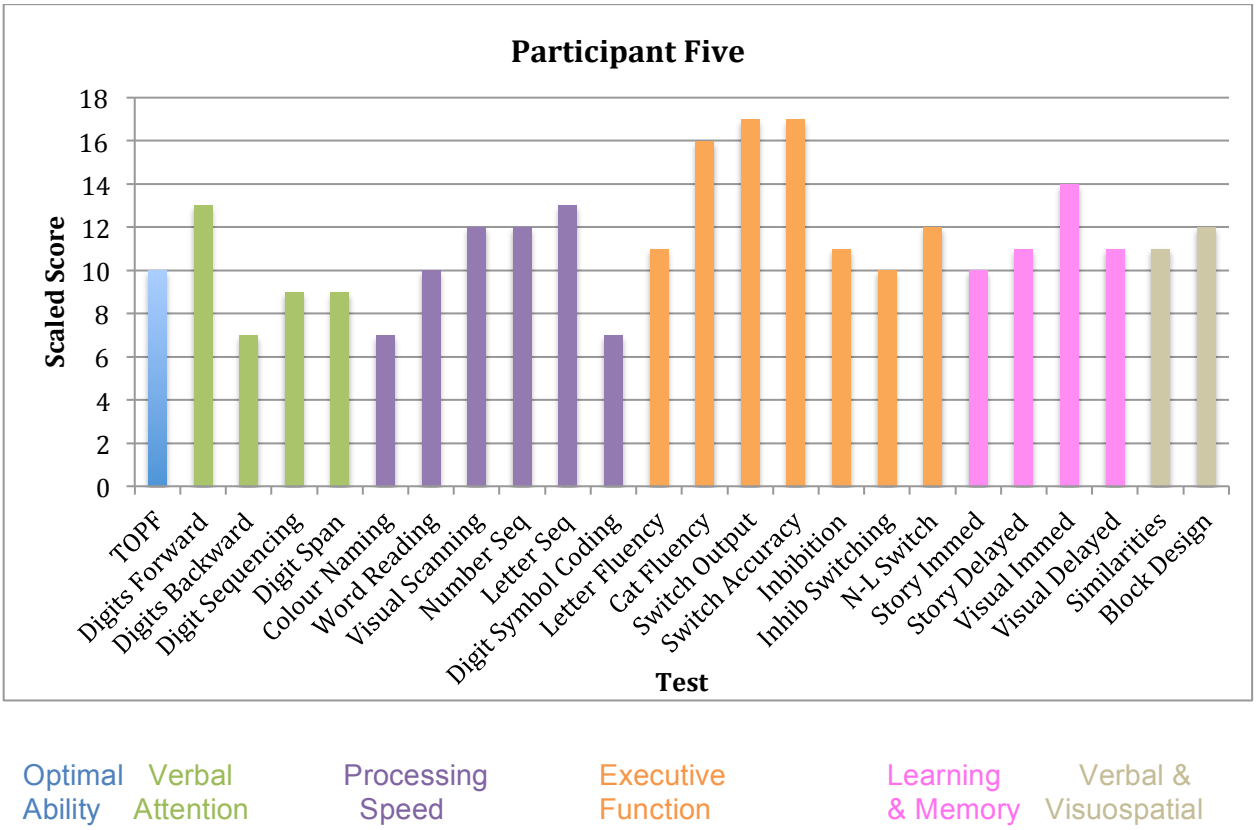

Figure 5. Scaled test scores for participant five.

Figure five shows intact skills in executive function, with particular strengths in Category Fluency, Switch Output and Accuracy and unaffected skills in learning and memory. For the domains of verbal attention and processing speed, there is less of a discernible pattern: there are relative weaknesses across all tests in Digit Span and also Colour Naming and Digit Symbol coding. This participant's scores for the TOPF did not offer much predictive power of their optimal ability across the administered tests, for which there was no distinctive pattern.

Although overall, most of this participant's profile was in the High Average range, there was considerable variability. The participant was seeing a psychologist for difficulties with low mood and anxiety at the time of testing, which could account for this. However, the recommendation was to monitor any concerns around cognitive function and this patient could be re-tested in the future.

3.7.6 Participant Six

Participant six was a 45-year-old British male. He worked as a chess coach and was educated to college level. Although he had been diagnosed in January 2016, he was being treated for retinopathy and treated by consultant and nurse specialist. Participant 6's Hba1c was 38.8% mmol and Lipid Profile: Chol 2.2% mmol; HDL 1.3% mmol; LDL 0.6% mmol; and TG 0.7% mmol.

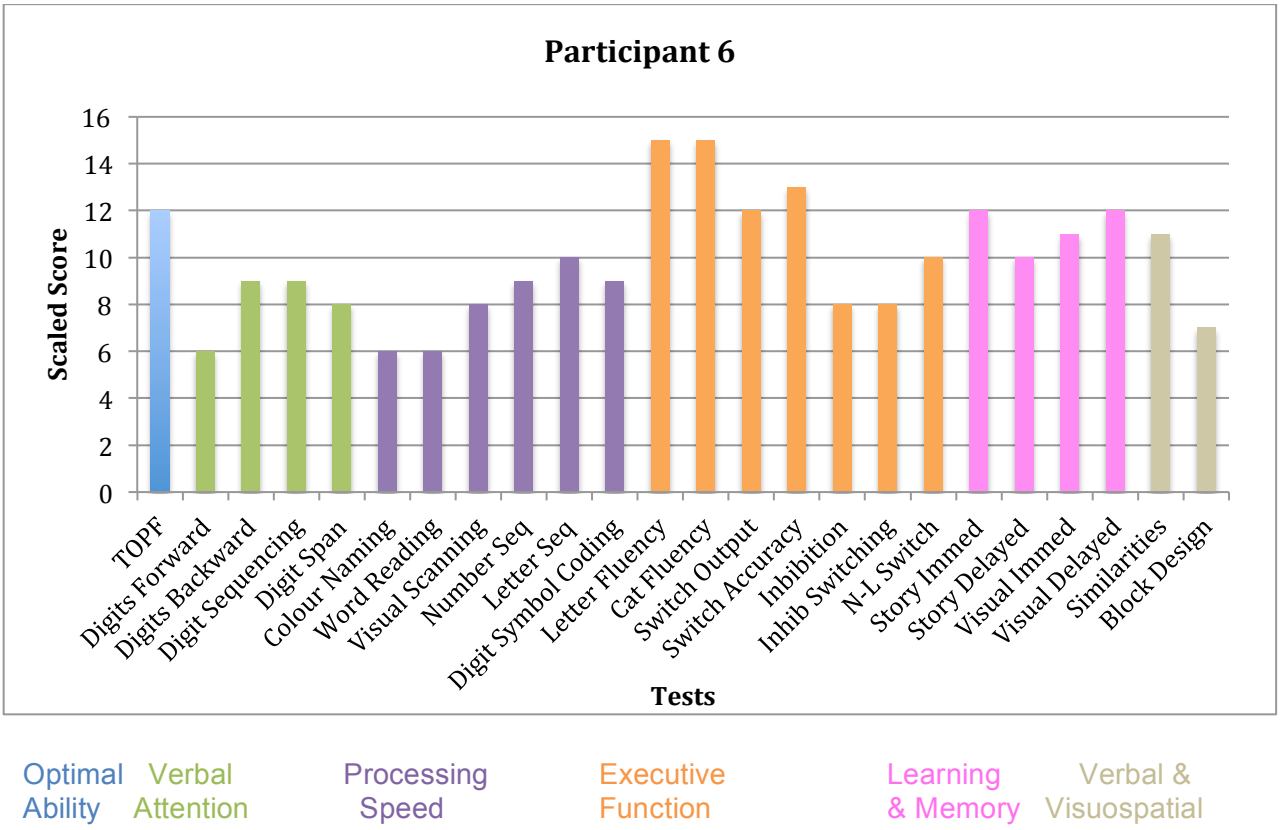

Figure 6. Scaled test scores for participant six.

As seen in figure six, participant six's performance showed impairment relative to his optimal ability across most of the scores on his test profile. His score on the TOPF indicates he has higher than average premorbid functioning. He did obtain relatively strong scores in some tests of executive function, namely Letter Fluency and Category Fluency. However, some other test scores in executive function showed a deficit, such as in the Inhibition and Inhibition Switching subtests. In addition, this weakness was also seen in the visuo-spatial construction test, Block Design. In summary, whilst participant six scored within

the Average range overall, there are some aspects of his profile that would be typical of someone with diabetes that were affected cognitively, especially relative to his optimal ability which tended to be higher than most of his test scores.

3.7.7 Participant seven

Participant seven was a 54-year-old British male who worked as a painter and decorator, and attended school until aged 15. He was diagnosed with Diabetes in 2007. His most recent Hba1c was 95% mmol and Lipid profile: Chol 3.9% mmol; HDL 1.0% mmol; LDL 2.3% mmol; and TG 1.4% mmol.

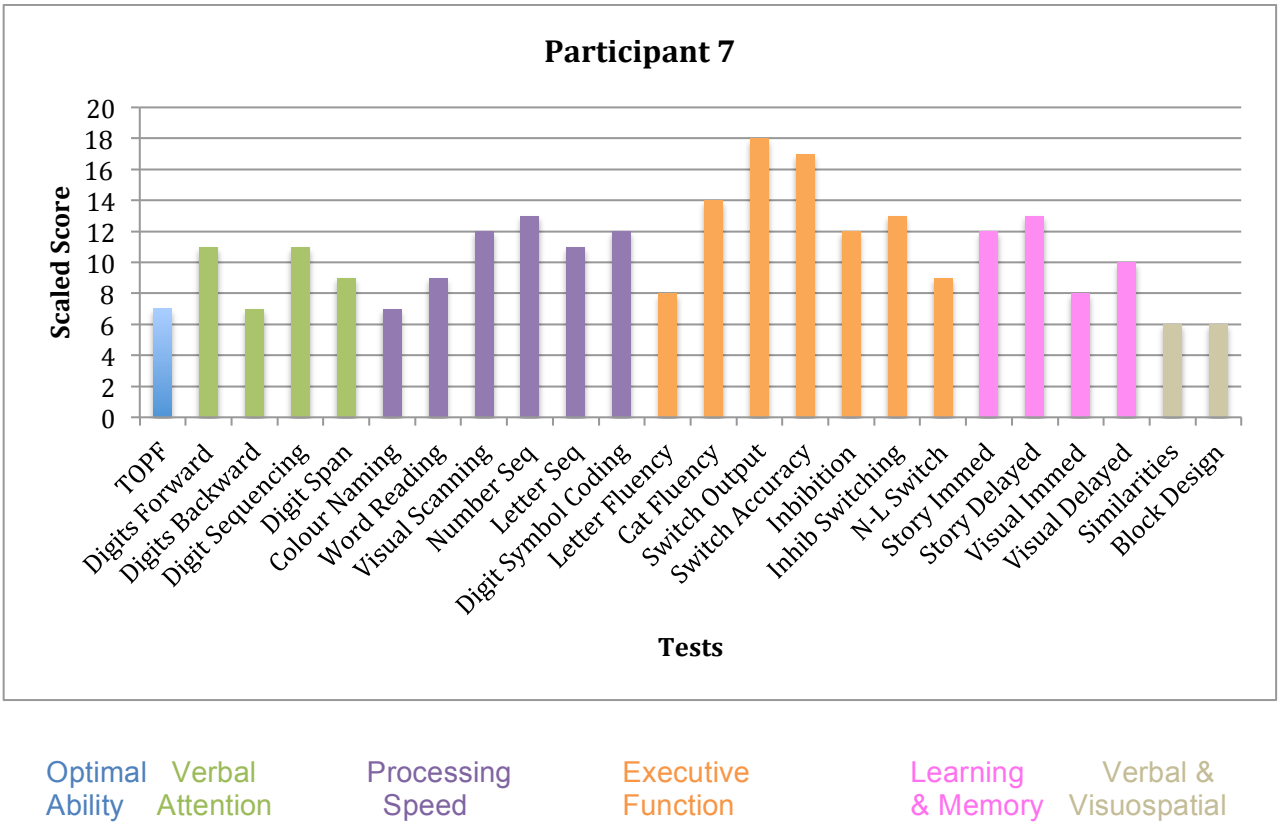

Figure 7. Scaled test scores for participant seven.

From figure seven, we can see this participant scored quite low on the TOPF. Most of the scores were variable although he had relatively intact skills for most domains, and verbal & visuospatial skills were a relative weakness. The majority of domains also show areas of relative strengths: attention - Digit Span Forward and Digit Span Sequencing; processing speed - Visual Scanning, Number Sequencing, Letter Sequencing and Digit Symbol Coding; executive function - Category Fluency, Switch Output and Accuracy and Inhibition Switching; and verbal learning and memory, Story Immediate and Story Delayed. This would not be a typical profile you may expect of someone with T2DM, especially

considering the high Hba1c they had, and how long they had the condition. Furthermore, this would indicate that optimal ability does not hold much predictive power for this participant in assessing potential impairment as a result of having diabetes.

3.7.8 Participant Eight

Participant Eight was a 50-year-old British born Asian female, who spoke English as an additional language alongside Bengali and Urdu. She completed one year of college and was employed as a catering assistant in a school. She had hypertension, which was being treated. She had a heart attack in 2015 and was being monitored for possible kidney problems. Her diabetes was diagnosed in 2005. Her Hba1c was 70% mmol and Lipid Profile: Chol 3.3% mmol; HDL 1.0% mmol; LDL 2.3% mmol; and TG 2.8% mmol.

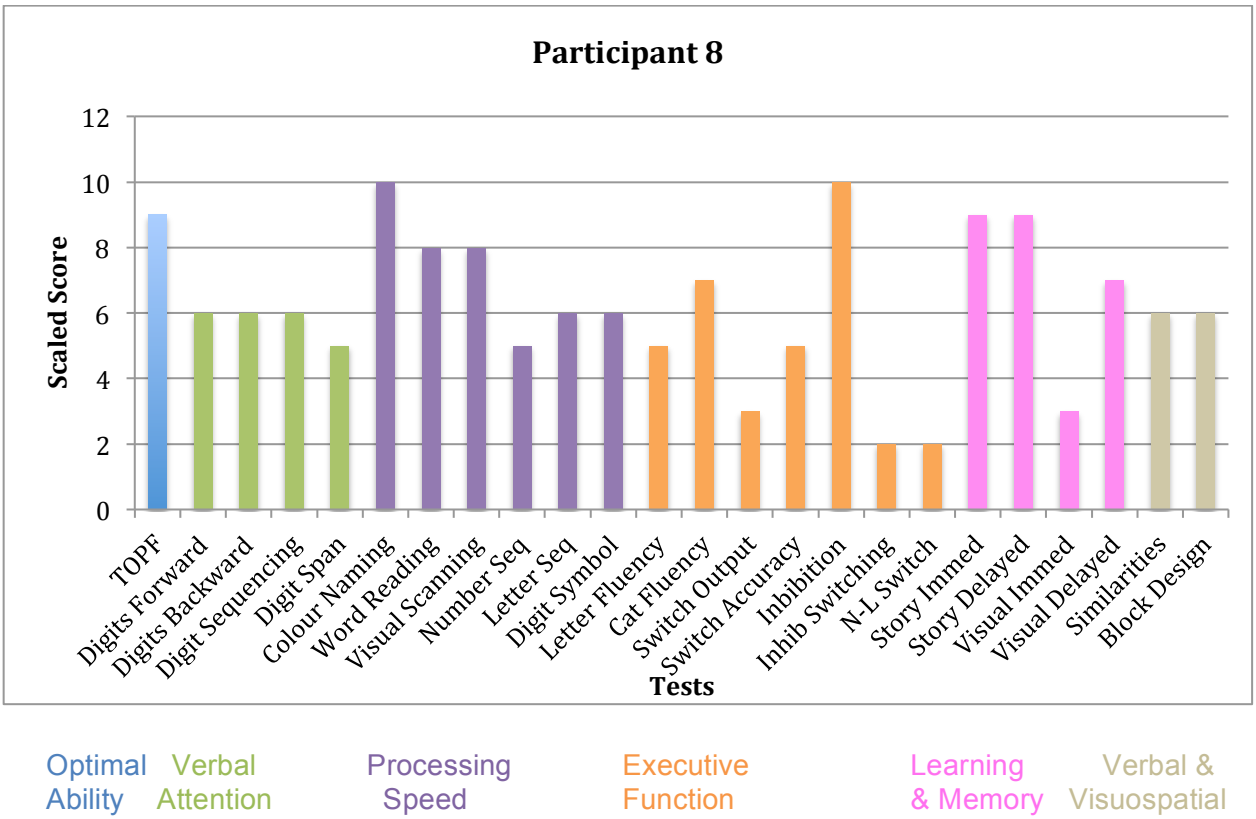

Figure 8. Scaled test scores for participant eight.

Figure 8 shows us that this participant had a varied profile across all domains. Compared to her test of optimal ability, it may indicate there have been relative declines across all domains apart from verbal and visuospatial. There was also some relative strength in processing speed, namely Colour Naming, and in executive function, specifically Inhibition. However, compared to participant eight's score in the TOPF, all scores were mostly below what would be expected based on her test of optimal ability, particularly her scores in verbal attention.

This may indicate some impairment relative to premorbid functioning, although some skills across the sequelae seem to be preserved.

3.7.9 Participant nine

Participant nine was a 55-year-old British female who was employed as a medical secretary, and completed her O-levels. She was diagnosed with diabetes in 2001. Her Hba1c was 63.9 and Lipid profile: Chol 4.4% mmol; HDL 1.0% mmol; LDL 1.5% mmol; and TG1.9% mmol.

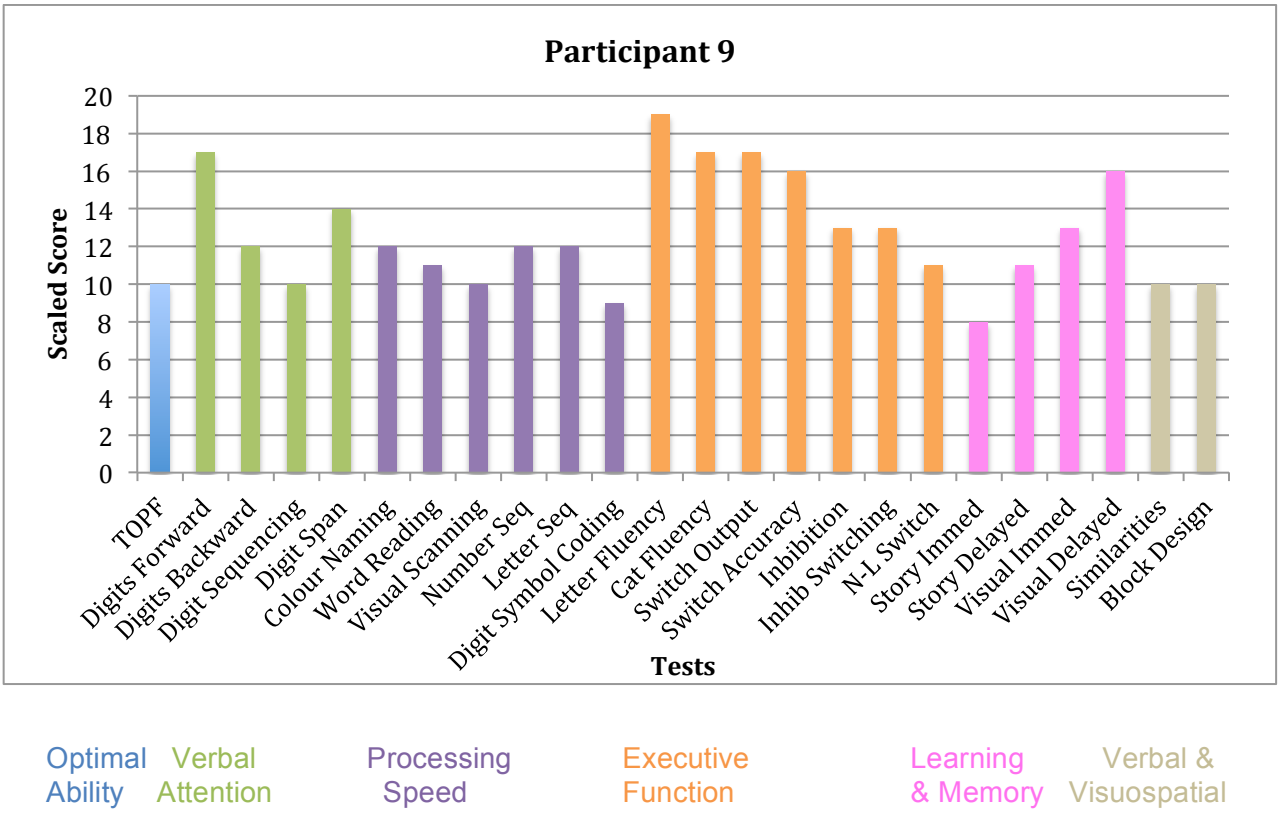

Figure 9. Scaled test scores for participant 9.

From figure nine, this participant achieved high scores in verbal attention in the Digits Forward subtest and she performed well in most tests of executive function but particularly in Letter Fluency. Many of her lower scores were in tests that measure processing speed or in immediate memory. However, these scores were relative to her scores of optimal ability and were equal or less than two standard deviations away than the TOPF score. The scores participant nine obtained show some aspects of a distribution that may be expected in people with T2DM e.g. lower in processing speed but due to the variability across all the domains, this could not be concluded with any degree of certainty. In addition,

this participant has done better than her score of optimal ability in the majority of the subtests administered across different domains.

3.7.10 Participant 10

Participant 10 was a 32-year-old British female. She was college educated and was looking for work as she had just moved into the area. Her diabetes was diagnosed in 2015 and her Hba1c was 106% mmol and Lipid Profile: Chol 3.7% mmol; HDL 1.7% mmol; LDL 1.4% mmol; and TG 1.3% mmol.

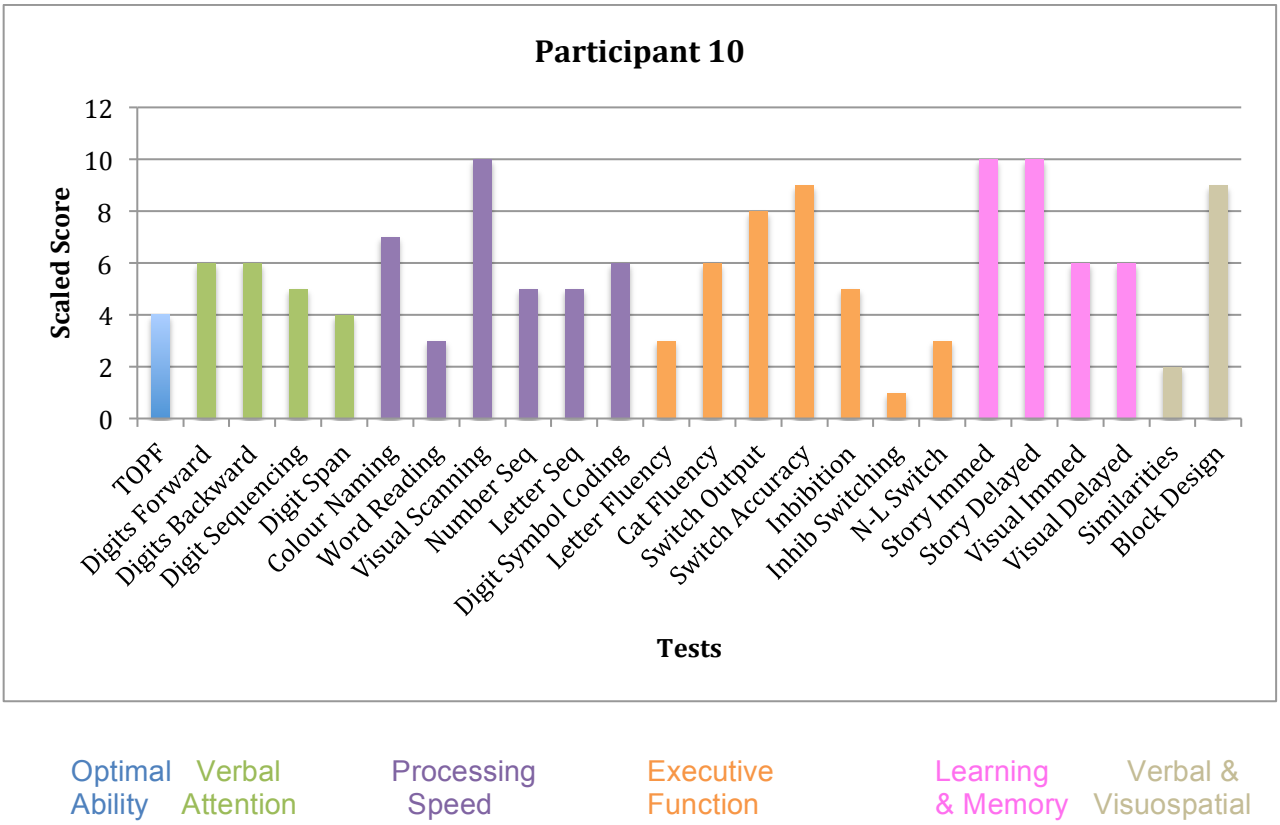

Figure 10. Scaled test scores for participant 10.

Overall, the cognitive profile for participant ten is typically in the Below Average or Impaired range. Whilst this is relative to her optimal ability scaled score, which was very low, there are some areas of relative strength but also weaknesses. This participant scored well in one test of processing speed, Visual Scanning, tests of learning and memory, specifically Story Immediate and Story Delayed, executive function in the Switch Accuracy subtest, and visuo-spatial construction, in Block Design. The areas that were most impaired were in tests of executive function, Letter Fluency, Inhibition Switching and Number-Letter Switching, and in verbal construction, Similarities. Interestingly, there seems to be no discernible

pattern about where this participants strengths lie, for example, there were relative strengths and weaknesses of tests of both language and visual skills. Typically, you may expect someone to perform well in one area and not in the other, rather than performing well and not so well in both. This may be explained in part by the life stresses that this participant was experiencing at the time of testing that were numerate and lengthy. I note she suffered a fractured skull aged five and said she had been diagnosed with dyslexia as a child.

3.8 Summary of Case Series Analysis

The exploration of the variables within the participant sample generates a different perspective on the potential impact of diabetes-related markers, as well as looking at patterns in individuals who were tested.

3.8.1 Comparison to TOPF

Overall, most participants scored in the average range or lower for the TOPF, but relative to this score, had very varied profiles across the range of subtests. Therefore, the scores on the TOPF may not be a valuable test by which to measure potential decline in T2DM.

3.8.2 Comparison to other group sample findings

Overall, the group sample showed that some tests of executive function were a relative strength and that some scores of attention and processing speed were a relative weakness. Looking at the individual case series, there were some participants that fitted with this profile but the majority did not. As described above, there was a lot of variability across the sample, showing patterns that were not easy to compare between participants. Yet, one aspect was discernible: most participants seemed to show some strength overall or relative to their optimal ability score in executive functioning, and specifically in the switch output task. This could indicate an issue with this particular task. On the whole, there was a lot of variability between and within the participant scores on the cognitive tests.

3.8.3 Summary

The case series analysis should be interpreted with caution, due to the small number of participants and the lack of statistical power this has. Furthermore, there are a number of factors that could have affected the performance on tests. For example, the clinical psychologist in the service was seeing three of the participants for difficulties with low mood and/or anxiety. In addition, one person had to be referred for urgent mental health assessment from testing, due to thoughts of suicide, which was picked up from the BDI. As difficulties like low mood and anxiety can impact on the speed in which we process information

(White, Myerson, & Hale, 1997), this can affect cognitive function overall (Hart & Kwentus, 1987; Ebmeier, Donaghey, & Steele, 2006). In addition, high levels of cholesterol are known to improve learning and memory (Schreurs, 2010) and so higher scores on some tests, may be indicative of this rather than intact function in some domains. Therefore, because of the complex interplay of the comorbidities in this population, we cannot attribute better or poorer performance on some tests to diabetes or factors associated with diabetes.

4. DISCUSSION

4.1 Summary

It has been established that diabetes can affect cognitive function, especially in older adults and the longer that one has the condition. Diabetes has become a global epidemic in health and economic terms. As such, great lengths are being taken to examine how diabetes can be stopped from progressing to the extent where it entails excessive treatment costs and causes premature death. Despite extensive research in the area, there is little consensus about the cognitive sequelae that are affected. With T2DM becoming the most common diabetes phenotype in children and adolescents in some parts of the world (Ke et al., 2015), concerns have been raised about how a condition of this nature will progress in people so young. This study set out to look at the potential impact of diabetes on cognitive function in younger adults, to explore whether the potential cognitive impact, is comparable in this population.

Ten individuals aged between 30 and 55 with T2DM were recruited from a London diabetes clinic and completed a battery of measures: this included demographics, medical history, health in the diabetes context, tests of cognitive function and measures of mood. Scores were closely examined for the relationships between cognitive variables, comparing the obtained scores to normative means and standard deviations. Finally, each participant was individually examined for his or her comparability to the group sample.

4.2 Population Demographics

The sample constituted a group of people with T2DM, of different ages, and each person was at a different stage of the condition, including the duration of their diabetes and how they were managing the condition e.g. dietetic input, type of medication, regular exercise. One person in the group had managed to keep their Hba1c level within an optimum range and others had comorbid conditions as well as their diabetes, which would suggest that any results should be interpreted

carefully as they may not be generalisable to other groups of people with diabetes.

Correlation analysis showed a relationship between Hba1c and tests of learning and memory and verbal-spatial construction, and cholesterol with a multitude of cognitive tests. Interestingly, no other diabetes-related health indicators were correlated with the cognitive tests, which is useful information considering the level of relatively good health within the sample.

4.3 Areas of Research Interest

4.3.1 Optimal Ability

The estimated optimal ability of the group was mostly in the average range. Although the sample was split 50:50 between people who spoke English as a first or a second or additional language, there were no obvious effects of language on performance.

When comparing optimal ability to health indicators related to diabetes, the TOPF was not correlated with values obtained from participants for Hba1c or cholesterol, nor any demographic aspects of the condition e.g. age, suggesting it is a robust measure in this sample.

As tests of optimal ability have not been used routinely in research into diabetes and cognitive function, the scores in this domain were compared to the other domains included in the test battery. No tests showed a significant impairment compared to scores of optimal ability. However, one test of executive function significantly improved following testing, indicating a possible anomaly with this sample.

4.3.2 Diabetes-related health indicators and cognitive function

Several variables related to diabetes were recorded: Hba1c, also known as the average glucose concentration in the blood over the last three months; lipid profile, which included total cholesterol, HDL, LDL and TG; and duration of diabetes. Only one of the participants had their levels of Hba1c within the

optimum range, but the majority of the sample did have lipid profiles within the recommended parameters.

Hba1c: was negatively correlated with tests of learning and memory. This may indicate that cognitive function can be affected by levels of glycated haemoglobin. This is consistent with research in the area, which suggests that higher levels of Hba1c were associated with worse cognitive function, accelerated memory loss, and overall decline (Yaffe et al., 2012; Marden et al., 2017).

4.3.2.1 Total cholesterol: was the variable related to diabetes, which showed the most significant values, but they were all positively correlated. Higher levels of total cholesterol were associated with higher scores on tests of attention, executive function, visuo-spatial construction and learning and memory. This could suggest that higher levels of cholesterol can protect cognitive function. Previous literature in the area has indicated that cholesterol can influence a series of learning and memory tasks but the nature of that influence is difficult to understand (Schreurs, 2010). However, whilst controversial, there is some evidence to suggest that higher cholesterol can improve cognition in certain tasks. Indeed, higher total cholesterol in mid-life is linked to poorer cognitive performance later in life but, if cholesterol levels lower after mid-life, this may indicate poorer cognitive status (Solomon et al., 2009). As noted previously, the relationship between cholesterol and cognition is not well understood, and any supporting inferential statistics from this study should be interpreted with caution.

4.3.2.2 HDL: showed a significant negative correlation with one test in the domain of processing speed (Word Reading). This indicates that lower HDL was associated with higher scaled scores on this test, which measures visual scanning and verbal output. Also known as ‘good’ cholesterol, lower levels of HDL would not be expected to correlate with tests of processing speed in this direction. As there is only one test that shows this relationship, it may not be useful to infer too much from this result. This is discussed further in limitations and recommendations.

4.3.2.3 LDL: positively correlated with one test of executive function, Inhibition. Whilst higher levels in the sample are related to better performance on this specific test, usually high levels of LDL are associated with higher risk of atherosclerosis or the build up of plaque in your arteries. Therefore, this correlation is not in the direction anticipated.

4.3.2.4 TG: was found to negatively correlate with a test of processing speed, Number Sequencing. For this sample, the lower the measured value of TG, the higher the obtained score in Number Sequencing. As TG are a type of fat in the blood, it is recommended that this is kept low. The relationship between the measured variables in this sample is in the direction predicted.

4.3.3 Relationship of demographic factors with cognitive function

The final area of interest was examining whether any areas of 'impairment' were related to demographic variables, such as duration of diabetes or age. However, by using scores of optimal ability as an indicator of impairment, there were no signs of change e.g. a lower score on subtests compared to scores of optimal ability. Therefore, no further statistical tests were undertaken to explore these variables further.

As mentioned previously, there was a significant improvement from scores of optimal ability compared to the scores obtained in Inhibition Switching. It is unusual to make an improvement of this nature but methodologically, there did not seem to be any errors in administration. This is discussed further in limitations and recommendations.

4.4 Case Series Analysis

From examining the individual profiles, the majority of participants did not follow the pattern of the group level analysis.

4.4.1 Tests of premorbid functioning

There was inconsistency in how useful the TOPF was as an estimator of premorbid ability in this sample: for the majority of participants it held little

predictive power. But for some participants it did seem to be an indicator of some kind of change relative to their TOPF score. However, because of the small sample, there were myriad different variables within that sample that could not be statistically controlled for, and it would be difficult to generalise beyond this sample.

4.4.2 Cognitive function

The observed distributions at a case level were also very varied and it was difficult to discern patterns between the cognitive test scores within the battery and also to the measured diabetes variables.

Examining participant data individually, most did not show the pattern of relative weakness in the cognitive domains that were analysed at the group level: namely in attention and processing speed.

However, executive function was an area that many participants performed well in. It could be that for this particular group there was something unique about those that were sampled, for example, being able to fit in testing around work commitments (for those that were employed) and remembering to come at the agreed time, as there were only a couple of issues during recruitment. Therefore, this could indicate people were already able in the domain of EF. Alternatively, people that chose and were able to attend testing may have been self-selecting, in that they were aware of their skill set and were motivated to attend an assessment.

4.4.3 Comparisons to previous work in the field

These findings are somewhat at odds with existing literature into the area, as most literature suggests that even in younger adults, there can be signs of cognitive impairment early in the pathogenesis of diabetes (Ruis et al., 2009). Some research indicates that in people with T2DM there are observable deficits across all cognitive domains compared to non-diabetic controls (Monette et al., 2014). Other research also indicates that there are a variety of domains that are affected but typically processing speed (Awad et al., 2004), attention (Manschot et al., 2006), and executive function (Mehrabian et al., 2012) may be impacted.

However, due to the complexity of diabetes and its co-occurring conditions, establishing how T2DM develops universally has been very challenging for researchers. Indeed, there has been wide variation in levels of understanding and contrasting conclusions made in literature in the area.

For some of the findings that were not related to research questions posed at the outset, previous research into cholesterol and memory has controversially found that higher levels of cholesterol can actually improve your memory (Schreurs, 2010). It is hypothesised this is linked to how the cholesterol in the blood improves the signals between brain synapses. In the current study, this finding was also supported. Whilst the effect size was not large, total cholesterol was implicated in better scores on learning and memory across several tests. Therefore, we may hypothesise that higher cholesterol seemed to protect learning and memory in people with T2DM in this sample.

4.4.4 Application to the research questions:

In summary, there were three main research questions posed were regarding optimal ability, the relationship between clinical markers of diabetes and cognition, and whether any impairment would be connected to health indicators related to diabetes.

In this particular study, using a test of optimal ability was not statistically useful to predict impairment in younger adults with T2DM. However, on an individual basis, there was some utility in scores of premorbid functioning as a baseline to compare their overall cognitive functioning.

Diabetes-related health indicators were not correlated with values of cognitive function in any distinct patterns, although cholesterol did seem to mediate cognitive performance more than any other variable.

Finally, there was no cognitive ‘impairment’ observed in this sample and so no further analyses were carried out on the data.

4.4.5 Summary

As this study is exploratory in nature, the inferences made should be taken lightly. It is not possible to infer if there is a potential window of preservation for cognitive function in younger adults with T2DM. However, some productive speculation can be made about the relationships between the variables: optimal ability may still be a useful predictor of cognitive function in people with T2DM, clinical markers of diabetes may mediate performance on cognitive tests, and that cognitive impairment could be present in larger sample of younger people with T2DM.

4.5 Study Limitations and Recommendations

4.5.1 Limitations

4.5.1.1 Sample size: the main issue for this study is the small number of participants that was recruited. Whilst great efforts were taken to promote recruitment, it was not possible to recruit as many participants as were intended, which was a minimum of 12 and ideally 20. Small sample size increases the likelihood of making a type II error (Field, 2013). This smaller sample also meant it was not possible to look at within group differences such as age, duration of condition, English as a first language or employment status.

4.5.1.2 Lack of a control group in the study design: this meant that it was not possible to compare the test performance of the people with T2DM to matched controls e.g. spouses, friends, hospital attendees. This would permit a comparison of the cognitive function to be made between the groups. Although the statistical tests selected were appropriate and accounted for one group for comparison, this may have meant that the findings had greater generalisability outside of this study.

4.5.1.3 Potential confounders: the clinicians in the service I recruited from had one main concern with the recruitment to the study – that it had the potential to 'derail' their interventions, especially if people were difficult to engage. Therefore, the clinicians acted as a potential barrier and confounder to recruitment in a non-

biased way i.e. access to more ‘typical’ patients that perhaps did not regularly attend and/or had problems managing their diabetes. In fact, one of the patients managed their diabetes so well that from recruiting to testing, had been discharged from the service. Therefore, I wonder whether the sample I had was less representative of the younger T2DM population in general.

4.5.1.4 Understanding of the test rubric: on the whole, participants seemed to understand what was expected of them in each test. There were occasions when despite being encouraged to ‘keep going’ or ‘do this task as quickly as you can’, the participants preferred to take their time with the tests, especially during tests of Executive Function such as the Trail Making Test. This approach seemed to fit more with their personal choice to meet the tasks at hand, e.g. being methodical and thorough, rather than a measure of their speed at completing the task (or lack thereof).

Cognitive tests are normed on Western populations, and some of my sample were not born or educated in the West. Cultural and educational differences can impact on scores in cognitive tests; therefore, the normative data that was used to make comparisons may not be equivalent (Fernandez & Marcopulos, 2008). Again, a larger sample size could have controlled for this.

4.5.1.5 Anomaly in test scores: some participants did particularly well in tests of executive function, specifically word generation. This was to the extent that record sheets were checked on several occasions for any errors of recording. The administration instructions were also examined for any possible errors in setting up the tasks. However, no errors were found.

4.5.1.6 Generalisability to other populations: due to where the sample was obtained in North London, it is questionable if it resembles a representative sample of younger age adults with T2DM. In Camden, the population is relatively young and very transient, and people do not tend to stay in the area. As a result, the incidence of T2DM is lower than the national average, and lower than the London average. A different London borough may have provided a more typical cognitive profile than the one obtained.

Another question is whether the sample obtained is a self-selected sample of people who are more able compared to other younger people with T2DM. For example, nearly all the group had finished school and those that had not were employed in a long-term capacity. The presence of a control group would have been helpful to address queries of this nature.

Finally, there are some cohort differences that mean that measuring cognitive functioning in younger adults and then comparing to older adults e.g. people over 55, may be difficult. For example, the school leaving age in England and Wales was raised from 14 to 15 in 1947 (people today aged 70 and over), and the compulsory school age became 16 in 1972, raised from 15 (people today aged 45 and over). The sample looked at people born between 1961 and 1962 onwards. Whilst it is acknowledged that normed scores are age scaled, there are substantial differences in required education that means it could impact on how comparisons could be made between these age groups.

4.5.2 Recommendations

4.5.2.1 Implications for existing theories: there is very little research available into optimal ability but the current research did fit with a smaller scale study involving older people with T2DM and carefully matched controls. Asimakopoulou et al., (2002) found there was no statistical difference between these groups on a battery of cognitive tests, including a test of premorbid functioning. However, larger samples are needed for both this and the afore-mentioned study.

Finding a relationship between Hba1c and tests of processing speed and attention is in keeping with existing research into the area (Awad et al., 2004; Manschot et al., 2006). I note that this was not a consistent pattern found within the data, so more testing would be needed to be establish this link. Furthermore, there has been recent research, which has found the connection between diabetes and impairment in attention inconclusive (Degen et al., 2016).

The findings related to lipid profile do have implications for the typical health messages being relayed regarding cholesterol. For example, we often hear about

increasing the good cholesterol in our diets. However, it was total cholesterol that mostly showed a significant effect size, not HDL, which is commonly referred to as ‘good’ cholesterol. Therefore, there may be grounds to consider this aspect of the findings in greater detail.

4.5.2.2 Adaptation of current theories: the findings from the current study have limited theoretical implications. Although the conclusions are potentially of interest, further research will need to be carried out to establish whether the correlations and relationships found can be repeated elsewhere. This would enable greater weight to be added to the results, which are at present, exploratory in nature.

4.5.2.3 Improving the current study: I would like to recruit more participants, aiming for the desired number of twenty participants that I set out to test.
It could be useful to reduce the number of variables being controlled for and reduce the age range. For example, recruiting young people with diabetes e.g. aged 35 and under, and use a prospective and longitudinal study, with one specific locus, such as processing speed and matched controls. By reducing the examined locus, it would speed up testing and make results quicker to score. In addition, using the new technology available to administer tests e.g. Q-Interactive on tablets, to quicken scoring and sending out results. Furthermore, there is a gap in the research into optimal ability and diabetes, as highlighted by the review by Wong et al. (2014). It would also be of clinical interest to produce an evidenced battery that could be administered quickly, that would not only help strengthen any possible link between cognition and diabetes but also be an aid to diabetes clinicians.

Whilst the presence of a control group is supposedly a ‘gold standard’ (Goldstein & McNeil, 2012), it does not always guarantee appropriate interpretation of findings. This can be because the control group differs too widely from the clinical sample (Bonato, Sella, Berteletti, & Umiltà, 2012). As such, recruiting a control from the clinical participants life would be most suitable, such as a partner, relative or friend, to minimise the variability between test and control participants.

4.5.2.4 Test battery: Psychometric assessments are based on constructs of cognition, as we understand it in the contemporary west. Cognitive domains are not discreet concepts and interact with each other. For example, tests of the domain of attention are rarely pure, but it is seen as a foundation for all other domains of cognition (Hebben & Milberg, 2009). Therefore, adapting the test battery may be a useful way to more sensitively test the different domains of cognitive function.

4.5.2.5 Cognitive Domains and Test Selection: The selected tests of executive function from the battery are regularly used in the literature (Wong et al., 2014; Vincent & Hall, 2015). However, it is important to acknowledge that whilst the tests selected were done so carefully, if different tests were chosen, it is likely to have produced different results.

The TOPF, WAIS-IV and WMS-III are all co-normed together (Holdnack, Zhou, Larrabee, Millis, & Salthouse, 2011), which means that the sample norms are derived from the same sample of test-takers. This develops more valid and reliable test scores and avoids assuming all norms from different test populations are equivalent. Whilst there is some contention in the literature about whether co-norming is required (Rohling et al. 2011), this approach was taken for caution.

Another example of a visuo-spatial test of EF could be the DKEFS Tower Test. This test was not selected as another aspect of the rationale for the test selection was to choose measures that could form part of a screening battery for clinicians from the diabetes team. Therefore, it was felt that tasks using paper-and-pen exercises would be more likely to be appropriate for this.

The DKEFS was selected because testing was being done on a presumed unimpaired sample. For example, by using the Number-Letter Switching task from the DKEFS instead of the Action Program Test from the BADS or the

Errands Task, we are testing very specific and different aspects of EF (and are not directly comparable). Therefore, we needed very sensitive tests to measure the presence of a defect, not the degree of impairment. This is why the DKEFS was selected, rather than the BADS, which presumes impairment. Nevertheless, it is acknowledged that some of the task focused tests e.g. Errands Task, may be more comparable to the tasks expected of someone in managing their diabetes.

Furthermore, the DKEFS subtests selected – Trail Making, Verbal Fluency, and Colour Word Test - assess specific aspects of Executive function – namely speed, motor and verbal inhibition/switching. It is not sensitive to all aspects of EF. Therefore, other tests in the DKEFS could have been selected. Again, consideration was given to the time taken to administer the battery. It was estimated with the tests already selected from the WAIS, WMS and DKEFS the battery would take 90 minutes to administer. Therefore, no additional tests were added to minimise the duration of testing due to the demands placed on participants.

Putting aside the rationale for selecting the chosen tests within the battery, alternative tests that could be used are the Behavioural Assessment of Dysexecutive Syndrome (BADS) (Wilson, Alderman, Burgess, Emslie and Evans, 1996), the DKEFS tower test or the Brixton Spatial Awareness Test (Burgess and Shalice, 1997). The BADS would be useful as it may be similar to some of the visuo-spatial/sequential tasks required of someone in their diabetes management. For example, blood testing before eating and then adjusting your food intake or medication regime accordingly. The DKEFS Tower Test or Brixton Spatial Awareness Test could assess working memory, and also induction of visuo-spatial rules, which could also be comparable to the demands of diabetes management. This is because you have to hold several things in mind, and follow rules depending on biological markers and instructions given my your clinician or pharmacist.

4.5.2.6 Statistical tests intended for analysis: at the beginning of the research process, the intention was to use General Linear Modelling, to explore a number of dependent variables with prediction of relationships for each. As there was no control group, this was not possible to use as only people with T2DM were assessed. However, future research could consider employing this method.

4.5.2.7 Approach to analysis: In the analysis, it was decided not to converge subtests that all tap the same underlying construct to compile an overall score for that domain. For example, this would involve combining scores from subtests such as Inhibition and Switching, to make a score of 'Executive function'. Approaching analysis this way ensured that collating the tests of a same domain did not obscure important differences within the sample. As mentioned previously, the intention behind this was it was assumed the population studied was unimpaired and so required tests to be sensitive to possible changes. As such, a collated score from several subtests for a domain may not have achieved this. However, it is useful to address what could be gained by taking such an approach and how it may be done.

By converging tests that tapped the same underlying construct, it could have evened out individual differences between different tests, and provided a more global score in each domain. This may have made the result more reliable as it could be compared more easily to other findings regarding the domain of executive function, and also be more stable. It would also have had more power as only contrasting two or three tests.

To achieve this, two approaches seemed most appropriate: first, within the DKEFS tests, you can combine the scores following the manual to obtain an average sequencing score, which can be contrasted with inhibition. Secondly, you can converge the domains by combining the scaled scores and divide by number of tests included in that combination. The first option would offer a validated and more specific approach to combining the scores, within the

construct of Executive Function; the second, a less robust but more comparable approach to other research within the area e.g. those that refer to executive function more globally than the approach taken within the thesis.

4.5.2.8 Future research: I would recruit non-diabetic controls to have a group to compare the diabetic participants to. Whilst we used a standardised mean and SD to compare the results to, which is similar to having a control group, it would add a more robust form of data analysis as a recruited group's mean and SD may be different to a set value.

I would also consider using a blood pressure monitoring and blood glucose measurement before and after testing. This would require training of the researcher or recruitment of a nurse. However, this would add another level of external validity to the study. In addition, other similar research has employed these methods (Salak Djokić et al., 2015). I would consider matching control participants on several characteristics, including premorbid ability.

4.6 Critical review

4.6.1 Personal reflections

Gaining NHS ethical approval was a difficult task, which took much longer than expected. This was in part to being unfamiliar with all the tasks that were expected in this process, and relying on fellow trainees, including those on different courses to help guide me. There was a change of Dean of the school part way through submitting the form for ethics approval and so having to bring two people up to speed with the process delayed matters, as did completing it over the summer holiday. If I were to approach this process again, I would attempt to get ethical approval much sooner and monitor the time when I sent off my application more wisely e.g. not over summer. The NHS site where I recruited people from took a while to support me with recruitment, and this took a considerable amount of liaison with the manager, in-house psychologist and

supervising clinical psychologist. By the end of the process, all staff were much more involved and responsive, which helped.

However, as my research was not meeting a clinical need and involved screening a population that were relatively well, the relevance of my work to the clinicians took some time for them to appreciate. Following completion of testing with their patients, members of the team were receptive to the suggestions I made about adapting their delivery of clinical information. For example, using visual prompts to aid understanding of their diabetes. However, when I followed up with them after testing of participants, the majority of clinicians did not believe the information would change their practice.

Many of the participants (and their referring clinicians at a later date) told me following completion of the measures how enjoyable they had found the tests. In addition, a lot of the participants were concerned about diabetes affecting the brain and how it could impact them. As such, some of my discussions with people were informal conversations about the problems associated with diabetes in older adults and what was understood in the literature about the condition in younger populations. No one in the sample had heard that diabetes was linked to cognitive changes in the brain in later life and this surprised me, as I would have thought this would have been discussed with people at risk. However, currently, the recommendations for cognitive screening are at a research not a clinical level (Sinclair et al., 2000; Cukierman et al., 2005). Diabetes UK, which is a source of information and advocacy for many people with diabetes, is yet to recommend that people be screened as part of their standardised diabetes care. Yet, in order to avoid disrupting the standardised diabetes care of patients in the clinic, I was steered away from recruiting the more complicated patients. Had there been any cognitive problems with these patients, arguably they would have benefited most from being tested.

Until patient and clinicians are aware of the possible cognitive changes that can happen as a result of diabetes - both related to and independent of cognitive aging - it will be challenging to galvanise more support and interest outside of research circles.

4.6.1.1 Practical applications of the research

Whilst this research has been exploratory in scope, it has been worthwhile for several reasons: firstly, to generate interest in an area of diabetes that has gained less interest outside of psychology and medicine; secondly, because of this reduced interest, becoming aware of potential difficulty in recruiting participants with diabetes for cognitive testing on a smaller scale. And finally, to generate some data that may indicate that, for some people with T2DM, there is no inevitability they will show cognitive impairment.

From the literature gathered and concluding themes drawn, the audiences that may benefit from this information are people with diabetes, clinicians working in diabetes – including nurses, podiatrists and dieticians – and researchers. This is because cognitive impairment in diabetes is a relatively unknown area compared to other areas of concern for the condition, and younger people with T2DM being impacted by cognition is even less known.

From the observed sample, it was found that executive functioning was better in this group, which was unexpected. In reflection of the performance of the sampled participants, I will outline both a possible biological and psychological formulation of this result: The biological reason for this could be that on the whole, the participants' diabetes was 'well-controlled'', to the extent that it did not affect their performance on the cognitive tests of executive function. It has been mentioned that the participants were selected through a triage of a clinician in the clinic. As such, those who were not managing their diabetes to a good enough standard were unlikely to be selected. Therefore, those who came to testing were unlikely to have issues with their diabetes care, and theoretically did not have issues with their executive function.

A possible psychological explanation of the unexpected result in executive function is that the people that chose to come to testing were self-selecting in two ways: firstly, in that they were able to attend and balance this with the demands

on their time e.g. job or parenting. This would indicate a real life example of adequate executive function. Secondly, they knew they were able to perform well on tests of this nature e.g. doing tasks requiring concentration and an ability to hold things in mind.

This explanation is not applicable to all participants. At the group level, executive function was a relative strength but individually some people did have poorer performance on some subtests of executive function. However, it is important to consider possible explanations for the unexpected result, which was found from testing. This could provide some useful data to provide to clinicians, namely that those that are managing their condition 'well', may be doing so because they have superior skills in executive function relative to other people with the condition. Therefore, it could be useful to consider measures that support improved executive function for those in clinic who are not managing their condition 'well', rather than treatment as usual. An example of this could be providing more support e.g. pill boxes that remind you to take medication, improved ways of asking clinicians questions e.g. a dedicated email address or developing an application with better diabetes-related information contained within it. Theoretically, interventions such as these could have implications for improved management and diabetic control for other patients' that are struggling with their regimen.

To date, I am unaware of a study has been done using the parameters chosen in this research. There are studies which assessed premorbid functioning/optimal ability, those that looked at younger adults e.g. around age 50, but none that combined those factors together and recruited primarily for a younger sample. Although the results from the analysis were not always in the direction expected, this is most likely attributable to the small sample size. Therefore, there is the possibility of finding a relationship with a larger sample and a suitable control group.

It will take some time to better understand the pathogenesis and impact of the condition becoming more common in younger adults and unfortunately, the most helpful part of diabetes care is prevention rather than working within the limits of what we know (Kumar & Singh, 2010). In the meantime, there have been calls to add cognitive dysfunction to the list of complications from chronic diabetes for over ten years (Sinclair et al., 2000; Cukierman et al., 2005), which I also support. These shifts in thinking can also help support clinicians on the frontline, especially with the additional knowledge of why cognition is so pivotal in diabetes.

4.7 Conclusion

This study explored premorbid functioning in younger adults with T2DM, and considered the participants' performance on a series of cognitive tests, for any associated patterns of cognitive functioning and/or diabetes-related health indicators.

In this particular sample, estimates of premorbid functioning were not useful for predicting performance on a set of tests that measure different cognitive function. Some relationships were found between health indicators connected to diabetes and cognition in the direction expected, including cholesterol and attention, executive function, visuo-spatial construction and learning and memory, and Hba1c and learning and memory and verbal-spatial construction.

The sample was also assessed for cognitive impairment using scores of optimal ability as a baseline measurement: there was no significant decrease between scores of optimal ability and cognitive tests. But, there was an improvement between a test of executive function and optimal ability, which based on previous literature, is considered anomalous.

As diabetes is a syndrome, its pathogenesis is multifactorial, which may be why cognitive impairment is not always present in people across the life span that have the condition. However, further research will be needed on a larger scale to establish the presence of cognitive impairment in younger adults with diabetes.

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6. APPENDICES

6.1 Appendix A: Participant Information Sheets for the Camden Research Site

Participant Information Sheet: v1.2 (1st September 2016) 203389
UNIVERSITY OF EAST LONDON
School of Psychology
Stratford Campus
Water Lane
London E15 4LZ

PARTICIPANT INFORMATION SHEET

Project Title: Cognitive function & Type 2 Diabetes: A Study Using Working Age Adults

Principal Investigator(s): Katy Lucas
E-mail: u1438310@uel.ac.uk
Telephone: 0208 223 4174

Invitation to Participate in a Research Study
The purpose of this letter is to provide you with the information that you need to consider in deciding whether to participate a research study. The study is being conducted as part of my Doctoral degree in Clinical Psychology at the University of East London.

I would like to invite you to take part in a research study. Before you decide whether to take part you need to understand why the research is being done and what it will involve. Please read through the following information carefully before deciding whether or not you would like to take part in the research. Talk to others about the study if you wish. If something needs clarification or you have any unanswered questions please do not hesitate to ask the researcher/research supervisor. The study is part of a Doctoral Degree in Clinical Psychology.

What is the purpose of the study?
The aim of the study is to try to understand how Type 2 Diabetes may affect people's ability to do certain tasks. This will help us understand if the condition in younger adults should be understood differently to other people with diabetes.

By understanding how this population may vary in their ability, services will consider making changes in order to improve people's treatment. Consequently, future practice may be altered to better meet the needs of younger adults with Type 2 Diabetes.

Why have I been invited?
You have been invited to take part in this study, as you have Type 2 Diabetes. I am interested in finding out how this condition might affect your performance on certain tests.

What will I be asked to do if I agree to take part?
The researcher will invite you for a meeting lasting between 90-120minutes. You will be asked to do some puzzles and answer some questions. The questions will be decided

before hand but will assess you on different skills you use everyday. It is not a meeting you would need to prepare for or need to know specific information.

Are there any disadvantages or risks to taking part?

Meeting with the researcher might make you more aware of your ability in certain areas. You may find certain tasks easier than others. However, if you feel any discomfort or distress, upon finishing the meeting you will be given the opportunity to talk to the researcher about them. Additionally, I would be happy to contact someone at the hospital or clinic for you to talk to or provide contact details of other organisations that can offer you support.

What will happen to the results of the research study?
The results of the study will be written up as a doctoral thesis and submitted for publication in a journal. In all written material of this study your identity will remain anonymous. The data will be stored for three years, following which time it will be shredded and disposed of.

Will the information I give be accessible to the clinicians/team in XXX Trust?
Only the researcher and her research supervisor will have access to the information you provide. Your clinicians will not be notified about your participation or the information that you have provided. Furthermore, your participation in this study will not affect your treatment. We can provide some information on your performance that could be useful for you about your cognitive strengths and abilities you could be supported with. However, if you feel any discomfort or distress, I would encourage you to seek support from either a clinician in the service or any of the organisations attached.

Will the information I provide remain confidential?
All the information provided by you is completely confidential; all paper information will be kept in a locked filing cabinet. Your personal information will be kept separate from the tasks you complete, which will be given a code with no identifying personal information attached to them. Your real name will not be used in the analysis or write up of the study. The answer sheets will be saved onto a computer system, which will only be accessible by the researcher and her supervisor through a password protected system.

Location: where will the meetings take place?
Meetings will take place at the clinic or hospital where you have your diabetes care or at the University of East London (Stratford campus) depending on your preference.

Do I have to take part?
No. It is entirely up to you. You are not obliged to take part in this study and you are free to withdraw at any time. Should you choose to withdraw from the study, you may do so without disadvantage to yourself and without giving any reason. This would not affect your usual care at the Camden Diabetes Service.

After May 8th 2017, all data will be anonymised and I will not be able to identify your data so removal of your data will not be possible. All data will be destroyed two years following completion of the research (completion date: May 2017) or following publication of the data, whichever date is earlier.

Who has reviewed the study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee to protect your safety, rights, well-being and dignity. In addition, ethics approval has been obtained from the University of East London.

Please feel free to ask me any questions. If you are happy to continue you will be asked to sign a consent form prior to your participation. Please retain this invitation letter for reference.

What if I have any complaints?
If you have a concern about any aspect of this study, you should ask to speak to the researcher who will do their best to answer your questions (contact number: 020 8223 4174). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure or the UEL Ethics Committee. Details can be obtained from the researcher/research supervisor below.

If you have any questions or concerns about how the study has been conducted, please contact the study's supervisor:

Matthew Jones Chester, School of Psychology, University of East London, Water Lane, London E15 4LZ.(Tel: 020 8223 4174. E-mail: m.h.jones-chesters@uel.ac.uk)
or
Chair of the School of Psychology Research Ethics Sub-committee: Dr. Mark Finn, School of Psychology, University of East London, Water Lane, London E15 4LZ.
(Tel: 020 8223 4493. Email: m.finn@uel.ac.uk)
or
The Patient Advice and Liaison Service at the Royal Free Hospital

The patient advice and liaison service for the Royal Free Hospital in the hospital's main reception.

The service is open from 10am to 4pm, Monday to Friday, except Wednesday, when the service is open from 10.30am to 4pm.

You can contact the team using the following details:

Tel: 020 7472 6446/6447; (020 7472 6445 - 24 hour answer phone)
Fax: 020 7472 6463
SMS: 447860023323 (Deaf, hard of hearing and hearing impaired patients only)
Email: rf.pals@nhs.net

Thank you in anticipation.

Yours sincerely,

Katy Lucas
November 2016

Thank you for taking the time to read this information sheet. Please keep for future reference.

6.2 Appendix B: NHS Research Ethics Committee Provisional Approval

Health Research Authority

West Midlands - Black Country Research Ethics Committee
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

23 August 2016

Ms Katy Lucas
Trainee Clinical Psychologist
Royal Free Hospital NHS Foundation Trust
University of East London: School of Psychology
Water Lane
LONDON
E15 4LZ

Dear Ms Lucas

Study title:	**Cognitive Function in Type 2 Diabetes: A Study Using Younger Adults**
REC reference:	**16/WM/0387**
IRAS project ID:	**203389**

The Proportionate Review Sub-Committee of the West Midlands - Black Country Research Ethics Committee reviewed the above application on 22 August 2016.

Provisional opinion

The Sub-Committee would be content to give a favourable ethical opinion of the research, subject to clarification of the following issues and/or the following changes being made to the documentation for study participants:

1. The methodology of the study must be clarified at section A13 of the application. A clear outline is requested to detail what the study plans to do, and how this will be achieved.
2. The study title must be corrected across the application and all study documentation to read; “Cognitive Function in Type 2 Diabetes: A Study Using
Working Age Adults”.
3. The Participant Information Sheet must be updated as follows;
    a. To contain the details of the local PAL Service.
    b. To amend the contradictory information given within the section titled;
    ‘Do I have to take part?’.
4. The Consent Form must be revised to;
    a. Condense the points and reduce the number of consent boxes.

b. Contain the name of the researcher.

5. A Protocol for what would happen in the event of incidental findings arising from the Beck Depression Inventory is requested.
6. The study exclusion criteria must be updated to include persons who are colour blind.
7. The reference to the sexual health clinic on page nine of the IRAS application should be explained or corrected as appropriate.
8. It is asked if the historical controls are valid for the ethnic groups likely participate.
9. Please clarify the expected time expense required of the assessments.

When submitting a response to the Sub-Committee, the requested information should be electronically submitted from IRAS. A step-by-step guide on submitting your response to the REC provisional opinion is available on the HRA website using the following link: http://www.hra.nhs.uk/nhs-research-ethics-committee-rec-submitting-response-provisional-opinion/

Please submit revised documentation where appropriate underlining or otherwise highlighting the changes which have been made and giving revised version numbers and dates. You do not have to make any changes to the REC application form unless you have been specifically requested to do so by the REC.

Authority to consider your response and to confirm the final opinion on behalf of the Committee has been delegated to the Chair.

Please contact the REC office if you need any further clarification or would find it helpful to discuss the changes required with the lead reviewer.

The Committee will confirm the final ethical opinion within 7 days of receiving a full response. A response should be submitted by no later than 22 September 2016.

Summary of discussion at the meeting

Social or scientific value; scientific design and conduct of the study

The Sub-Committee considered the proposal difficult to follow and the methodology unclear. A clear outline was requested at section A13 of the application to detail what the study plans to do, and how this will be achieved.

The Sub-Committee presumed the reference to the sexual health clinic on page nine of the application was included in error, and requested this reference be explained or corrected.

The Sub-Committee noted the incorrect study title was used within the IRAS application and across study documentation, and requested that this be corrected throughout to read; “Cognitive Function in Type 2 Diabetes: A Study Using Working Age Adults”.

The Sub-Committee discussed the colour test to be conducted as part of the cognitive assessments and commented that this is not appropriate for participants who are colour blind, adding that the use of such persons would give false results. The Sub-Committee agreed that the study exclusion criteria should be updated to include this group.

The Sub-Committee commented on the number of assessments required of the participants, and questioned if the proposed 90 minutes is realistic. The Sub-Committee added that the time varies across the application from 90-120 minutes and requested the expected time expense be clarified.

The Sub-Committee considered the established norms of the tests and the ethnic diversity in Camden. The Sub-Committee stated that norms do need ethnic origin correction, and noted that this is not considered in the application. The Sub-Committee asked if the historical controls are valid for the ethnic groups likely to participate.

Care and protection of research participants; respect for potential and enrolled participants' welfare and dignity

The Sub-Committee queried what would happen in the event of incidental findings arising from the Beck Depression Inventory scale, and requested that a protocol for this be submitted.

Informed consent process and the adequacy and completeness of participant information

The Sub-Committee discussed the Participant Information Sheet and noted the two paragraphs under the section "Do I have to take part" are contradictory and must be revised.

The Sub-Committee noted that the document is without reference to the local PAL Service, and requested details of this be added.

The Sub-Committee reviewed the Consent Form and asked for the name of the researcher to be added to the document. The Sub-Committee considered there to be too many boxes on the Consent Form, and agreed that the points should be condensed.

Documents reviewed

The documents reviewed were:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Academic Indemnity Insurance]	Version 1	01 August 2015
Interview schedules or topic guides for participants [Protocol]	1.1	04 August 2016
Interview schedules or topic guides for participants [Protocol]	1.1	14 August 2016
IRAS Application Form [IRAS_Form_12082016]		12 August 2016
IRAS Checklist XML [Checklist_15082016]		15 August 2016
Letter from sponsor [Confirmed Registration]	Version 1	27 June 2016
Other [Debrief Sheet]	1.1	05 August 2016
Other [Research Proposal - Initial Academic Feedback]	1	05 August 2016
Other [DKEFS - Colour Word Inference]	1	15 August 2016
Other [DKEFS - Trail Making]	1	15 August 2016
Other [DKEFS - Verbal Fluency]	1	15 August 2016
Other [Test of Premorbid Functioning]	1	15 August 2016
Other [WAIS - Coding]	1	15 August 2016

Other [WAIS - Block Design]	1	15 August 2016
Other [WAIS - Digit Span]	1	15 August 2016
Other [WAIS - Similarities]	1	15 August 2016
Other [WMS - Visual Reproduction and Logical Memory]	1	15 August 2016
Other [Becks Anxiety Inventory]	1	15 August 2016
Other [Becks Depression Inventory]	1	15 August 2016
Participant consent form [Participant Consent Form]	1.1	14 August 2016
Participant information sheet (PIS) [Participant Information Sheet]	1.1	05 August 2016
Referee's report or other scientific critique report [Email and Letter Confirming Academic Approval of the Study]	1.0	05 August 2016
Research protocol or project proposal [Amended Research Proposal]	Version 1	05 August 2016
Sample diary card/patient card [Record Form]	1.1	05 August 2016
Summary CV for Chief Investigator (CI) [CV]	Version 1	13 June 2016
Summary CV for supervisor (student research) [Summary CV for supervisor]	1.0	05 August 2016

Membership of the Committee

The members of the 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 and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

16/WM/0387	**Please quote this number on all correspondence**

Yours sincerely

PP

Reverend Keith Lackenby
Acting Chair

Email: nrescommittee.westmidlands-blackcountry@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Professor Neville Punchard*
Miranda Rosenthal, Royal Free Hospital NHS Foundation Trust

West Midlands - Black Country
Research Ethics Committee

Attendance at PRS Sub-Committee of the REC meeting on 22 August 2016

Committee Members:

Name	*Profession*	*Present*	*Notes*
Mrs Chris Bell	Board Member	Yes	
Reverend Keith Lackenby (Acting Chair)	Reverend	Yes	
Dr Tony Zalin	Expert Member	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Miss Lindsey Wallace	REC Assistant

6.3 Appendix C: Letter to Address Issues from REC Board

Katy Lucas
11 Springfield
Avenue Road
London
SE25 4ED
16th September 2016

Reverend Keith Lackenby
Acting Chair
West Midlands – Black Country REC
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Dear Reverend Lackenby,

RE: Amendments to IRAS 203389 "Cognitive Function in Type 2 Diabetes: A Study Using Working Age Adults"

Thank you for the guidance received on 23rd August 2016 in respect of the ethics form. Based on the feedback, I wanted to address each item in turn:

1. The methodology of the study must be clarified at section A13 of the application. A clear outline is requested to detail what the study plans to do, and how this will be achieved.
I have updated this section, including providing an outlined summary of what the study plans to do, and how this will be achieved.

2. The study title must be corrected across the application and all study documentation to read; "Cognitive Function in Type 2 Diabetes: A Study Using Working Age Adults".
This has been updated to read: Cognitive Function & Type 2 Diabetes – A Study Using Working Age Adults.

3. The Participant Information Sheet must be updated as follows;
a. To contain the details of the local PAL Service.
This has been updated. Please see the attached PIS.

b. To amend the contradictory information given within the section titled; 'Do I have to take part?'
This has been updated on the Participant Information Sheet to clarify the difference between withdrawing participation from the study and when it is not possible for anonymised data to be removed. Please see the updated Participation Information Sheet.

4. The Consent Form must be revised to;
a. Condense the points and reduce the number of consent boxes.

The points have been condensed and the number of consent boxes reduced. Please see the updated Consent Form.

b. Contain the name of the researcher.
This has been updated. Please see the updated Consent Form.

5. A Protocol for what would happen in the event of incidental findings arising from the Beck Depression Inventory is requested.
This has been added into A13 and reads:

The BDI score will be computed and, if above 25, items subscribed to will be reviewed items. For high scores participants will be advised in session that their scores is high and suggestive of mood problems. Participants will be provided with information on referring to their local psychology (IAPT) service, and to seek the advice of their GP for further help. If participants subscribe to item 9 (risk of harm to self) a risk assessment will be undertaken. The results will be discussed with the supervisor to determine the most appropriate action (e.g., to contact referring clinician, duty social worker or GP). If the RA suggests an immediate risk to self or others, advice will be given on attending to see their GP and/or A&E services.

6. The study exclusion criteria must be updated to include persons who are colour blind.
The exclusion criteria in the IRAS form has been updated.

7. The reference to the sexual health clinic on page nine of the IRAS application should be explained or corrected as appropriate.
This has been removed as it was submitted in error.

8. It is asked if the historical controls are valid for the ethnic groups likely participate.
The neuropsychological tests used are valid for primary speakers of English (first or second language English speakers who use English as their main language) except for the TOPF. It is unfortunately the case that no neuropsychological test set exists for non-Western cultural groups that have the required sensitivity for this study. The results in individual cases will be interpreted in context and with caution. However, no person will be excluded from the study on the basis of their cultural and/or ethnic identity.

9. Please clarify the expected time expense required of the assessments.
This had been updated in all sections and documentation of the application to read 90-120 minutes.

I hope there is sufficient information in the letter and the proposal to address the suggestions made. I look forward to hearing from you.

Best wishes,

Katy Lucas

6.4 Appendix D: NHS Research Favourable Opinion Letter

Health Research Authority

West Midlands - Black Country Research Ethics Committee

The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

23 September 2016

Miss Katy Lucas
School of Psychology, University of East London
Stratford Campus
Water Lane
E15 4LZ

Dear Miss Lucas

Study title:	**Cognitive Function & Type 2 Diabetes: A Study of Working Age Adults**
REC reference:	**16/WM/0387**
IRAS project ID:	**203389**

Thank you for your letter of 20/09/2016, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Georgia Copeland, nrescommittee.westmidlands-blackcountry@nhs.net

Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials

will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the 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).

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" above).

Approved documents

The documents reviewed and approved by the Committee are:

Document	*Version*	*Date*
Covering letter on headed paper [Letter to Address Amendment Requests from REC board]	1.1	20 September 2016
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Academic Indemnity Insurance]	Version 1	01 August 2015
Interview schedules or topic guides for participants [Protocol]	1.1	14 August 2016
IRAS Application Form [IRAS_Form_20092016]		20 September 2016
IRAS Application Form XML file [IRAS_Form_20092016]		20 September 2016
IRAS Checklist XML [Checklist_20092016]		20 September 2016
Letter from sponsor [Confirmed Registration]	Version 1	27 June 2016
Other [Research Proposal - Initial Academic Feedback]	1	05 August 2016
Other [DKEFS - Colour Word Inference]	1	15 August 2016
Other [DKEFS - Trail Making]	1	15 August 2016
Other [DKEFS - Verbal Fluency]	1	15 August 2016
Other [Test of Premorbid Functioning]	1	15 August 2016
Other [WAIS - Coding]	1	15 August 2016
Other [WAIS - Block Design]	1	15 August 2016
Other [WAIS - Digit Span]	1	15 August 2016
Other [WAIS - Similarities]	1	15 August 2016

Other [WMS - Visual Reproduction and Logical Memory]	1	15 August 2016
Other [Becks Anxiety Inventory]	1	15 August 2016
Other [Becks Depression Inventory]	1	15 August 2016
Other [Debrief Sheet]	1.2	20 September 2016
Participant consent form [Participant Consent Form]	1.3	20 September 2016
Participant information sheet (PIS) [Participant Information Sheet]	1.3	20 September 2016
Referee's report or other scientific critique report [Email and Letter Confirming Academic Approval of the Study]	1.0	05 August 2016
Research protocol or project proposal [Amended Research Proposal]	Version 1	05 August 2016
Sample diary card/patient card [Record Form]	1.2	20 September 2016
Summary CV for Chief Investigator (CI) [CV]	Version 1	13 June 2016
Summary CV for supervisor (student research) [Summary CV for supervisor]	1.0	05 August 2016

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

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
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

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 HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

16/WM/0387	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

Reverend Keith Lackenby
Chair

Email: nrescommittee.westmidlands-blackcountry@nhs.net

Enclosures: *"After ethical review – guidance for researchers"*
Copy to: *Professor Neville Punchard*
Dr Paul Chadwick, Royal Free London Hospital NHS Foundation Trust

6.5 Appendix E: HRA Approval Letter

NHS
Health Research Authority

Miss Katy Lucas
School of Psychology, University of East London Stratford Campus
Water Lane E15 4LZ
Email: hra.approval@nhs.net

21 October 2016

Dear Miss Lucas,

Letter of HRA Approval

Study title:	**Cognitive Function & Type 2 Diabetes: A Study of Working Age Adults**
IRAS project ID:	**203389**
REC reference:	**16/WM/0387**
Sponsor	**University of East London**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

1. *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
2. *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
3. *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details

and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators",* issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please email the HRA at hra.approval@nhs.net.
Additionally, one of our staff would be happy to call and discuss your experience of HRA Approval.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **203389**. Please quote this on all correspondence.

Yours sincerely

Steph Blacklock
Senior Assessor

Email: hra.approval@nhs.net

Copy to: *Professor Michael Seed, University of East London, Sponsor Contact*
Dr Paul Chadwick, Royal Free London Hospital NHS Foundation Trust, Lead R&D Contact

Appendix A - List of Documents

The final document set assessed and approved by HRA Approval is listed below.

Document	*Version*	*Date*
Covering letter on headed paper [Letter to Address Amendment Requests from REC board]	1.1	20 September 2016
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Academic Indemnity Insurance]	Version 1	01 August 2015
Interview schedules or topic guides for participants [Protocol]	1.1	14 August 2016
IRAS Application Form [IRAS_Form_20092016]		20 September 2016
IRAS Application Form XML file [IRAS_Form_20092016]		20 September 2016
Letter from sponsor [Confirmed Registration]	Version 1	27 June 2016
Other [Debrief Sheet]	1.1	05 August 2016
Other [DKEFS - Colour Word Inference]	1	15 August 2016
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Other [WAIS - Block Design]	1	15 August 2016
Other [WAIS - Digit Span]	1	15 August 2016
Other [WAIS - Similarities]	1	15 August 2016
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Other [Becks Depression Inventory]	1	15 August 2016
Other [Debrief Sheet]	1.2	20 September 2016
Participant consent form [Participant Consent Form]	1.3	20 September 2016
Participant information sheet (PIS) [Participant Information Sheet]	1.3	20 September 2016
Referee's report or other scientific critique report [Email	1.0	0 August 2016

and Letter Confirming Academic Approval of the Study]		5
Sample diary card/patient card [Record Form]	1.2	2 September 0 2016
Summary CV for Chief Investigator (CI) [CV]	Version 1	1 3 June 2016
Statement of Activities	1.0	2 1 October 2016
Schedule of Events	1.0	2 1 October 2016

Appendix B - Summary of HRA Assessment

This appendix provides assurance to you, the sponsor and the NHS in England that the study, as reviewed for HRA Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England to assist in assessing and arranging capacity and capability.

For information on how the sponsor should be working with participating NHS organisations in England, please refer to the, *participating NHS organisations*, *capacity and capability* and *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* sections in this appendix.

The following person is the sponsor contact for the purpose of addressing participating organisation questions relating to the study:

Miss Katy Lucas u1438310@uel.ac.uk

HRA assessment criteria

Section	HRA Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	No comments
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	Statement of Activities and Schedule of Events provided for use with the participating organisation.

4.2	Insurance/indemnity arrangements assessed	Yes	Applicant has confirmed that a valid insurance certificate will be in place prior to study start. Where applicable, independent contractors (e.g. General Practitioners) should ensure that the professional indemnity provided by their medical defence organisation covers the activities expected of them for this

Section	HRA Assessment Criteria	Compliant with Standards	Comments
			research study
4.3	Financial arrangements assessed	Yes	There is no external funding acquired for this study and therefore no funds distributed to participating organisations.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	Not Applicable
5.3	Compliance with any applicable laws or regulations	Not Applicable	Not Applicable
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	No comments
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	Not Applicable
6.3	Devices – MHRA notice of no objection received	Not Applicable	Not Applicable
6.4	Other regulatory approvals and authorisations received	Not Applicable	Not Applicable

Participating NHS Organisations in England

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.

This is a single site, student, qualitative study with one participating organisation and therefore one site type. The study aim is to begin a preliminary exploration of cognitive function in people with T2DM aged 18-55Y. Interested participants will undergo an interview, standardised tests and receive a profile of their cognitive strengths and areas for development.

Confirmation of Capacity and Capability

This describes whether formal confirmation of capacity and capability is expected from participating NHS organisations in England.

Participating NHS organisations in England that are identifying participants and conducting interviews will be expected to formally confirm their capacity and capability to host this research.

- Following issue of this letter, participating NHS organisations in England may now confirm to the sponsor their capacity and capability to host this research, when ready to do so. How capacity and capacity will be confirmed is detailed in the *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* section of this appendix.
- The Assessing, Arranging, and Confirming document on the HRA website provides further information for the sponsor and NHS organisations on assessing, arranging and confirming capacity and capability.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and the minimum expectations for education, training and experience that PIs should meet (where applicable).

Student researcher is acting as the local collaborator for the participating organisation. GCP training is not a generic training expectation, in line with the HRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken
Student researcher will require a letter of access if no other honorary accesses are already in place with the participating organisation.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England to aid study set-up.
• The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

6.6 Appendix F: Letter of Access from the Royal Free Hospital

Royal Free London NHS
NHS Foundation Trust

Royal Free Hospital
Pond Street
London
NW3 2QG

Tel: 020 3758 2000

24/10/2016
Dear *Katy Janet Lucas*
Project ID: 9901 (Please quote in all correspondence)
REC Ref: 16/WM/0387
UKCRN ID:
IRAS ID: 203389
Title: Cognitive Function & Type 2 Diabetes: A Study of Working Age Adults

Letter of access for research

This letter should be presented to each participating organisation before you commence your research at that site. The participating organisation is Royal Free London NHS Foundation Trust.

In accepting this letter, each participating organisation confirms your right of access to conduct research through their organisation for the purpose and on the terms and conditions set out below. This right of access commences on 24/10/2016 and ends on 10/05/2017unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from the Royal Free London NHS Foundation Trust. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving confirmation from the individual organisation(s) of their agreement to conduct the research.

The information supplied about your role in research at the organisation(s) has been reviewed and you do not require an honorary research contract with the organisation(s). We are satisfied that such pre- engagement checks as we consider necessary have been carried out. Evidence of checks should be available on request to the organisation(s).

You are considered to be a legal visitor to the organisations premises. You are not entitled to any form of payment or access to other benefits provided by the organisation(s) or this organisation to employees and this letter does not give rise

to any other relationship between you and the organisation(s), in particular that of an employee.

While undertaking research through the organisation(s) you will remain accountable to your substantive employer but you are required to follow the reasonable instructions of the organisation(s) or those instructions given on their behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by the organisation(s) in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with the organisations policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with the organisation(s) in discharging its/their duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on the organisations premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

If you have a physical or mental health condition or disability which may affect your research role and which might require special adjustments to your role, if you have not already done so, you must notify your employer and each organisation prior to commencing your research role at that organisation.

You are required to ensure that all information regarding patients or staff remains secure and strictly confidential at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the organisations premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that the organisation(s) do not accept responsibility for damage to or loss of personal property.

This organisation may revoke this letter and any organisation(s) may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to

the interests and/or business of the organisation(s) or if you are convicted of any criminal offence. You must not undertake regulated activity if you are barred from such work. If you are barred from working with adults or children this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity and you MUST stop undertaking any regulated activity immediately.
Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

No organisation will indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in the Royal Free London NHS Foundation Trust and the the Royal Free London NHS Foundation Trust R&D office.

Yours sincerely

world class expertise local care
www.royalfree.nhs.uk

Dominic Dodd, chairman David Sloman, chief executive

Neil Hubbard
Research Portfolio Manager
Royal Free London NHS Foundation Trust

cc: HR department of the substantive employer
PI

6.7 Appendix G: UEL Ethical Approval

School of Psychology Research Ethics Committee

NOTICE OF ETHICS REVIEW DECISION

For research involving human participants

BSc/MSc/MA/Professional Doctorates in Clinical, Counselling and Educational Psychology

REVIEWER: Rachel Tribe

SUPERVISOR: Matthew Jones Chesters

COURSE: Professional Doctorate in Clinical Psychology

STUDENT: Katy Lucas

TITLE OF PROPOSED STUDY: Cognitive Function in Type 2 Diabetes Mellitus: A study using younger adults

DECISION OPTIONS:

1. **APPROVED:** Ethics approval for the above named research study has been granted from the date of approval (see end of this notice) to the date it is submitted for assessment/examination.

2. **APPROVED, BUT MINOR AMENDMENTS ARE REQUIRED BEFORE THE RESEARCH COMMENCES** (see Minor Amendments box below)**:** In this circumstance, re-submission of an ethics application is not required but the student must confirm with their supervisor that all minor amendments have been made before the research commences. Students are to do this by filling in the confirmation box below when all amendments have been attended to and emailing a copy of this decision notice to her/his supervisor for their records. The supervisor will then forward the student's confirmation to the School for its records.

3. **NOT APPROVED, MAJOR AMENDMENTS AND RE-SUBMISSION REQUIRED** (see Major Amendments box below)**:** In this circumstance, a revised ethics application must be submitted and approved before any research takes place. The revised application will be reviewed by the same reviewer. If in doubt, students should ask their supervisor for support in revising their ethics application.

DECISION ON THE ABOVE-NAMED PROPOSED RESEARCH STUDY
(Please indicate the decision according to one of the 3 options above)

Approved

Minor amendments required *(for reviewer)*:

This sounds like an interesting and important study. I would ask that the trainee and supervisor have checked that NHS ethics is not needed for this study, as it doesn't appear to be mentioned, unless I missed it? As the supervisor is an experienced clinician and researcher I guess this this has been done, but it be good for clarification to be given. If this is done and the appropriate procedure followed I am happy with this study. I couldn't find the age range for the study, but younger adults means over 18, so the participants would not be classified as vulnerable people.

Major amendments required *(for reviewer):*

ASSESSMENT OF RISK TO RESEACHER *(for reviewer)*

If the proposed research could expose the researcher to any of kind of emotional, physical or health and safety hazard? Please rate the degree of risk:

- [ ] HIGH
- [ ] MEDIUM
- [X] LOW

Reviewer comments in relation to researcher risk (if any):

Reviewer *(Typed name to act as signature)*: Prof R Tribe

Date: 1.7.16

This reviewer has assessed the ethics application for the named research study on behalf of the School of Psychology Research Ethics Committee

Confirmation of making the above minor amendments *(for students)*:

I have noted and made all the required minor amendments, as stated above, before starting my research and collecting data. Student's name *(Typed name to act as signature):* Student number: Date: *(Please submit a copy of this decision letter to your supervisor with this box completed, if minor amendments to your ethics application are required)*

PLEASE NOTE:

*For the researcher and participants involved in the above named study to be covered by UEL's insurance and indemnity policy, prior ethics approval from the School of Psychology (acting on behalf of the UEL Research Ethics Committee), and confirmation from students where minor amendments were required, must be obtained before any research takes place.

*For the researcher and participants involved in the above named study to be covered by UEL's insurance and indemnity policy, travel approval from UEL (not the School of Psychology) must be gained if a researcher intends to travel overseas to collect data, even if this involves the researcher travelling to his/her home country to conduct the research. Application details can be found here: http://www.uel.ac.uk/gradschool/ethics/fieldwork/

6.8 Appendix H: UREC Sponsorship Confirmation Letter

7th November 2016

Dear Katy,

Project Title:	**Cognitive Function & Type 2 Diabetes: A Study of Working Age Adults**
Researcher(s):	**Katy Lucas**
Principal Investigator:	**Katy Lucas**

I am writing to confirm that the application for the aforementioned NHS research study reference **16/WM/0387** has received UREC ethical approval and is sponsored by the University of East London.

The lapse date for ethical approval for this study is **7th November 2020**. If you require UREC approval beyond this date you must submit satisfactory evidence from the NHS confirming that your study has current NHS R&D ethical approval and provide a reason why UREC approval should be extended.

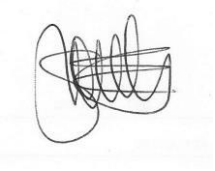
Please note as a condition of your sponsorship by the University of East London your research must be conducted in accordance with NHS regulations and any requirements specified as part of your NHS R&D ethical approval.

Please confirm that you will conduct your study in accordance with the consent given by the Trust Research Ethics Committee by emailing researchethics@uel.ac.uk.

Please ensure you retain this approval letter, as in the future you may be asked to provide proof of ethical approval.

With the Committee's best wishes for the success of this project.

Yours sincerely,



Catherine Fieulleteau
Research Integrity and Ethics Manager
For and on behalf of
Dr Lisa Mooney
University Research Ethics Committee (UREC)
Research Ethics
Email: **researchethics@uel.ac.uk**

6.9 Appendix I: Consent Form for Camden Research Site

Consent Form. Version 1.2 (1st September 2016)

UNIVERSITY OF EAST LONDON

Consent to participate in a research study

How do working age adults with Type 2 Diabetes do on tests of Cognitive Ability? What is the cognitive ability of working age adults with Type 2 Diabetes?

Please initial box:

I confirm that I have read and understood the information sheet for this study and been given a copy of the information sheet to keep. ☐

I have been given the opportunity to ask questions, to which I have received satisfactory answers. ☐

I understand what is going to happen and what I am being asked to do. ☐

I understand that only the researcher, Katy Lucas, and her research supervisor will have access to the research data, to which I give my permission. ☐

I understand what will happen to the data once the research has been completed. ☐

I understand that my involvement in this study is voluntary and that I may withdraw at any time if I wish to do so, and this will not affect the standard of care I continue to receive by the service. ☐

I hereby fully and freely agree to take part in the research, which has been fully explained to me.

Participant's Name (BLOCK CAPITALS) …….

Participant's Signature ……..

Researcher's Name (BLOCK CAPITALS) ……..

Researcher's Signature ……

Date: ……..

6.10 Appendix J: Interview Protocol

Protocol Version 1.1 (4th August 2016) IRAS 203389

UNIVERSITY OF EAST LONDON
School of Psychology
Stratford Campus
Water Lane
London E15 4LZ

Schedule and Procedural Information for Administered Questionnaires

Tests will be administered in the same order and a break will be added at the same time (or whenever the participant requires) to the schedule.

Introductions
Check preferred name, explain confidentiality, consent and right to withdraw at any point. Confirm length of assessment.

Rapport Building
Journey to session, and how they feel physically.

Brief Demographic Interview
Check DOB, education and occupational history, when they left school, highest level of education, left or right handedness.

Medical History
Diabetes-Related Health Indicators: duration of diabetes, hypertension status, CVD status, stroke status, other relevant information.
Cognitive Event History Head injury, stroke, and muscular sclerosis

Testing:

1. Test Of Premorbid Functioning (TOPF) – this test is to estimate a level of cognitive and memory functioning before the onset of illness, in this case diabetes. This involves pronouncing words that have atypical grapheme to phoneme translations, and accordingly success depends on prior knowledge of the items. Participants will be required to pronounce as many words as they can from a displayed list of words of increasing difficulty.

2. WAIS Block Design
In this test of perception and construction, the participant has a limited time in which to view a design and use red-and-white blocks to recreate the design.

3. WAIS Similarities
In this test of verbal reasoning, the participant is presented with two words and is required to say how they are alike (related).

4. WAIS Digit Span

This test of short-term stores and working memory has 3 components. For digit span forwards, the participant is read a sequence of numbers and recalls the numbers in the same order. For Digit Span Backwards, the participant is read a sequence of numbers and recalls the numbers in reverse order. For Digit Span Sequencing, the participant is read a sequence of numbers and recalls the numbers in ascending numerical order.

5. WAIS Digit Symbol Coding
A test of processing speed: the participant is required to use a key/legend and copies symbols that are paired with numbers within a specific time limit.

6. WMS Visual reproduction I
This test assesses memory for nonverbal stimuli. A series of five designs is shown, one at a time, for 10 seconds each. After each design is presented, the examinee is asked to draw the design from memory.

7. WMS Logical Memory I
This assesses narrative memory under a free recall condition. Two short stories are orally presented. The examinee is asked to retell each story from memory immediately after hearing it.

9. Comfort Break Offered

10. DKEFS Verbal Fluency
This is a measure of mental set and shift (flexibility). The participant is asked within a time limit to give (a) words that begin with a specific letter of the alphabet, then (b) items from specific categories (e.g., animals) and then (c) to switch between two categories (e.g., animals and boys names).

11. DKEFS Trail Making Test
This is a measure of sequencing and alternation. The participant is asked to (a) join up circles on a printed page (a) in number order (i.e., 1-2-3) and then (b) in alphabetical order (i.e., A-B-C) and then (c) to switch between numbers and letters but sticking to order (i.e., 1-A-2-B etc.).

12. DKEFS Colour-Word Inference
This is a measure of the ability to inhibit a well-learned response (reading). It has four conditions (a) simple colour naming (b) colour-word reading (c) ink- colour naming (inhibition, in which colour words are printed in incongruent inks) and (d) switching between naming the ink versus reading the word.

13. Beck Depression Inventory (BDI)
The BDI is a 21-question multiple-choice self-report inventory measuring low mood and symptoms of depression, occurring over the last week.

14. Beck Anxiety Inventory
The BAI is a 21-questios multiple-choice self-report inventory measuring the symptoms of anxiety, occurring over the last week.

15. WMS Visual Reproduction II

This assesses long term visual-spatial memory free recall. The examinee is asked to draw the designs shown during the immediate recall condition from memory in any order.

16. WMS Logical Memory II
This assesses long-term narrative memory with free recall and recognition tasks. The examinee is asked to retell both stories from the immediate condition. Then the examinee is asked yes/no questions about both stories.

6.11 Appendix K: Participant Debrief Sheet

Debrief Sheet and Sources of Information and Support: Version 1.2 (20th September 2016) IRAS 203389

UNIVERSITY
OF EAST LONDON
School of Psychology
Stratford Campus
Water Lane
London E15 4LZ

PARTICIPANT DEBRIEF SHEET

Project Title: Cognitive function & Type 2 Diabetes: A Study Using Working Age Adults

Principal Investigator(s): Katy Lucas
E-mail: u1438310@uel.ac.uk
Telephone: 0208 223 4174

Thank you for your participation in the study
This debrief sheet is to note our appreciation for your time and effort for taking part in the study today. We have reiterated a few key points of information but if you have any questions that are not covered below, please do not hesitate to ask.

What will happen to the results of the research study?
The results of the study will be written up as a doctoral thesis and submitted for publication in a journal. In all written material of this study your identity will remain anonymous. The data will be stored for three years, following which time it will be shredded and disposed of.

Who should I contact if I need additional support?
Whilst we hope that we have provided sufficient information and support, should you want more support or if you experience any distress or concern as a result of participating in your research, we have provided information about who to contact:

Diabetes Service
As the Diabetes Service in Camden referred you, you can contact the service with questions about your condition. The clinicians in the service are aware of the research and so are receptive to questions following your participation. Please contact Katy Lucas for more information

Psychology Service
There is a psychology service attached to the diabetes service, and clinicians in the Camden Diabetes service can make referrals to psychology at your request. Please contact Katy Lucas for more information.

Diabetes UK
Diabetes UK is the leading UK charity that cares for, connects with and campaigns on behalf of all people affected by diabetes. They have a careline open Monday to Friday for people with diabetes, their friends, family and carers 0345 123 2399. They also have a website https://www.diabetes.org.uk/, which also details their local support groups amongst other support.
https://www.diabetes.org.uk/How_we_help/Local_support_groups/

In an emergency, please contact your GP or go to your nearest A+E department

6.12 Appendix L: Blank Record Form

Cognitive Function in Young Adults with T2DM

Researcher: Katy LUCAS. Email: u1438310@uel.ac.uk

v1.2 (1st September 2016) IRAS: 203389

Record Form

Demographic & Clinical Details

ID:		Exam by:	
DoB:		Exam Date:	
Age:		Exam Location:	
Primary Language:		Gender:	
Years Education:		Handedness:	

Medical History

Head Injury:	Stroke:	MS:
Details/Other:		

Relevant Medical Values

Duration of T2DM:		LDL:	%/2 mmol
Recent Hba1C:	%/mol	HDL:	%/mmol
Chol – Total:	%/mmol	TRI:	%/mmol

Inclusion/Exclusion Check

History of high blood pressure:	History of cardiovascular disease:
History of severe mental illness:	History of colour blindness:

Domain	Test	Raw	Scaled	%ile	Label
Optimal Ability	TOPF-UK				
Verbal Attention	Digits Forward				
	Digits Backward				
	Digits Sequencing				
	Digit Span Overall				
Processing Speed	Digit-Symbol Coding				
	Colour Naming				
	Colour Word Reading				
	Visual Scanning				
	Number Sequencing				
	Letter Sequencing				
Executive Function:	Letter Fluency				
	Category Fluency				
	Switch Output				
	Switch Accuracy				
	Inhibition				
	Inhibition Switching				
	Number Letter Switching				
Learning & Memory: Verbal	Story Immediate				
	Story Delayed Recall				
	Story Recognition				
Learning & Memory: Visual	Visual Immediate				
	Visual Delayed Recall				
	Visual Recognition				
Verbal & Visuo-spatial	Similarities				
	Block Design				
Mood	Beck Depression				
	Beck Anxiety				

6.13 Appendix M - Conversion Table for Scaled Scores

Scaled	Standard	T-score	%ile	Label	%ile Range
19	145	80	99.9	Very-Superior	>98th
18	140	77	99.6		
17	135	73	99.0		
16	130	70	97.7	Superior	91-98th
15	125	67	95.2		
14	120	63	90.9		
13	115	60	84.1	High Average	75-90th
12	110	57	74.8		
11	105	53	63.1	Average	50-74th
10	100	50	50.0		
9	95	47	36.9		25-49th
8	90	43	25.3		
7	85	40	15.9	Low-Average	10-24th
6	80	37	9.1		
5	75	33	4.8	Below-Normal	2-9th
4	70	30	2.3		
3	65	27	1.0	Impaired	<2nd
2	60	23	0.4		
1	55	20	0.1		