Assessing specific cognitive deficits associated with dementia in older adults with Down's syndrome: a London based study

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I, Amanda Sinai, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Background: Dementia in older adults with Down's syndrome is common. People with Down's syndrome often have specific cognitive deficits, affecting prefrontal, hippocampal and cerebellar regions. A cognitive assessment battery has been developed (called the Arizona Cognitive Test Battery, ACTB), which assesses cognitive function in these areas. These tests have not yet been validated in older adults with Down's syndrome.

Methods: This study aimed to assess the use of the ACTB in older adults with Down's syndrome and establish its validity in testing for dementia. Participants with Down's syndrome aged 45 and over were assessed. Participants took part in a 2-3 hour assessment which included tests on a touchscreen computer tablet as well as standard table-top tests.

Results: 50 participants with Down's syndrome were recruited. Of these, 19 had a diagnosis of dementia or possible dementia. Most participants were able to attempt most of the tasks, although some tasks had a large number of participants at floor. There were significant differences between the dementia and no dementia groups on CANTAB Simple Reaction Time, Verbal Fluency and Object Memory tasks.

Conclusions: In general, most of the tasks in the ACTB can be used in older adults with Down's syndrome and have mild to moderate concurrent validity when compared to tabletop tests and carer ratings, although this varies on a test by test basis. Although, the ACTB can be used in older adults with Down's syndrome, it has not been shown to clearly detect differences between people with Down's syndrome who have early stage dementia and those who do not have dementia. Suggestions are made regarding which of the tests assessed in this study are most useful when assessing cognitive skills in older people with Down's syndrome. It is hoped that this research will help in the development of appropriate cognitive tests for older adults with Down's syndrome.

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Chapter 1. Background

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1.1 Overview

In this chapter, I will begin by defining the terminology and definitions that I will be using in this thesis. I will go on to discuss the epidemiology, aetiology and physical characteristics of Down's syndrome, before summarising the relevant literature on the cognitive profile of Down's syndrome. I will then consider the epidemiology, aetiology, cognitive profile and clinical features of dementia in Down's syndrome. I will conclude by discussing some of the most common measures used to assess the cognitive deficits that may be associated with dementia in people with Down's syndrome, which is the basis of this research study.

1.2 Abbreviations

ACTB - Arizona Cognitive Test Battery. This is a battery of several tests that has been developed to measure specific cognitive skills in people with Down's syndrome.

APO-E – Apolipoprotein E

APP – Amyloid Precursor Protein. This is a protein that is associated with the development of Alzheimer's disease.

BP – Blood Pressure

BPM – beats per minute (relating to pulse measurement)

BRI – Behavioural Regulation Index (a subscale on the BRIEF)

BRIEF – Behaviour Rating Inventory of Executive Function. This is a carer rated assessment of executive function.

CANTAB – Cambridge Neuropsychological Test Automated Battery. These are a set of computer-based neuropsychological tests designed to test specific cognitive skills.

CAMCOG-DS – Cambridge Cognitive Examination – Down's Syndrome

CI – Confidence Interval

CVA – Cerebro-Vascular Accident.

DAT – Dementia of Alzheimer's Type. This is a term often used to describe Alzheimer's disease in individuals with Down's syndrome.

DLD – Dementia Questionnaire for people with Learning Disabilities. This was formerly known as the Dementia Questionnaire for persons with Mental Retardation (DMR).

DSM – Diagnostic and Statistical Manual of Mental Disorders. Operationalised criteria for the diagnosis of mental disorders published by the American Psychiatric Association.

DVT – Deep Vein Thrombosis

GP – General Practitioner

GWAS – Genome Wide Association Studies

ICD – International Classification of Diseases. Operationalised criteria for the classification of diseases published by the World Health Organisation.

IED – Intra-Extra Dimensional Shift task (one of the CANTAB neuropsychological tests)

IQ – Intelligence Quotient. This is often used as a measure of general intelligence.

K-BIT – Kaufman Brief Intelligence Test

MOT – Motor Screening Task (one of the CANTAB neuropsychological tests)

NAID – Neuropsychological Assessment of age related cognitive deficits for people with Intellectual Disability.

NEPSY - developmental NEuroPSYchological assessment. A battery of tests of cognitive abilities designed for children.

NHS – National Health Service

PAL – Paired Associates Learning task (one of the CANTAB neuropsychological tests)

PAS-ADD – Psychiatric Assessment Schedule for Adults with Developmental Disabilities

PICALM – Phosphatidylinositol binding Clathrin Assembly Protein. The gene for this protein has been shown to affect age of onset of dementia in people with Down's syndrome.

SD – Standard deviation

SPSS – Statistical Package for the Social Sciences

SRT – Simple Reaction Time task (one of the CANTAB neuropsychological tests)

STM – Short Term Memory (a subscale on the DLD)

1.3 Terminology and definitions

Cognition The word cognition is used by many different disciplines, including psychiatry, psychology, linguistics and computer science, and can have different meanings according to the context. Dierssen has recently described cognition as "the process or processes whereby an organism gains knowledge or becomes aware of events or objects in its environment and uses that knowledge for comprehension and problem solving" (Dierssen, 2012). In this thesis, I have used Dierssen's description of cognition, which encompasses processes such as attention, perception, calculation, reasoning, learning and memory.

Dementia is characterised by a decline, from baseline functioning, in memory and other cognitive and daily living skills. In ICD-10, a decline in emotional control, motivation or social behaviour is also required for a diagnosis (World Health Organisation, 1992).

Both ICD-10 (World Health Organisation, 1992) and DSM-IV (American Psychiatric Association, 2000) use the term dementia. In DSM 5, a new category of Major Neurocognitive Disorder, is used to describe dementia and its aetiological sub-types (American Psychiatric Association, 2013). As this study was conducted when ICD-10 and DSM-IV were in use, I will be using the ICD-10 and DSM-IV definitions of dementia in this thesis.

Alzheimer's disease is a type of dementia which can present insidiously with a decline in memory, with subsequent gradual deterioration of brain functions, including decline in other cognitive skills.

Intellectual disability is defined by a significant impairment in both intellectual and adaptive functioning, which has arisen within the developmental period (i.e. before the age of 18) (World Health Organisation, 1992). In the UK, it can be known as learning disability. Intellectual disability has previously been known as mental retardation or mental handicap. Both ICD-10 and DSM-IV use the term mental retardation, although in both

research and clinical practice, this term is no longer commonly used. In DSM 5, the terminology has changed to Intellectual Disability (Intellectual Developmental Disorder).

Incidence is a term given to the number of new cases of a disease or disorder in a population within a given time period.

Prevalence is a term given to the number of cases of a disease or disorder in a population.

1.4 Introduction

Over the past century, improvements in health and social care have enhanced the quality of life and life expectancy for the general population as well as for people with intellectual disability. In the 1930s, the mean life expectancy of people with intellectual disability was estimated at 18.5 years of age, which increased to 66 years of age by the 1990s (Braddock, 1999). Improvements in medical care, in particular cardiac surgery, have led to a substantial rise in the estimated life expectancy for people with Down's syndrome. For example, in the USA, it has been estimated that the median age at death of people with Down's syndrome with additional congenital heart defects increased from 0 to 18 years or more in the early 1990's (Yang et al, 2002) and it has been estimated that the number of people with Down's syndrome in the Netherlands over 40 years old has doubled since 1990, to reach a peak of around 4600 in 2010 (de Graaf et al, 2011).

People with Down's syndrome are therefore now much more likely to be living into older adulthood. This is associated with increased rates of age-related conditions, including dementia, which, in turn may impact not only the individual affected, but also may have social, financial and emotional consequences for families, carers and other social support systems, e.g. local and national level healthcare and social welfare systems (Strydom and Sinai, 2014).

Making a diagnosis of dementia in a person with Down's syndrome can be particularly challenging, especially if a baseline level of cognitive functioning has not been well documented, as an important characteristic of dementia is a decline from baseline function (Strydom and Sinai, 2014). Although many of the causes and features of dementia in people with Down's syndrome are similar to that of Alzheimer's disease in the general population, there are some differences, for example, dementia in people with Down's syndrome is more likely to present with frontal lobe related features (Ball et al, 2006a) and is associated with a higher rate of epilepsy. For this reason, the term

Dementia of Alzheimer's type (abbreviated to DAT) is often used to describe Alzheimer's disease in individuals with Down's syndrome.

It is still not entirely clear why adults with Down's syndrome have such a high risk of developing dementia, and there is ongoing research to try to identify more of the risk and preventative factors. The most accepted hypothesis is that it is related to the amyloid precursor protein (APP) gene, which is located on Chromosome 21 and therefore triplicated in people with Trisomy 21 (Rumble et al, 1989).

By understanding more about dementia in Down's syndrome, we hope to also be able to understand more about dementia in the general population. I will discuss Down's syndrome and dementia in further detail in the remainder of this chapter.

1.5 Down's syndrome

1.5.1 Epidemiology

Down's syndrome is the most common genetic cause of intellectual disability and, in the USA, has been estimated to have a rate of approximately 14 per 10,000 live births (Parker et al, 2010). Down's syndrome, first described by Langdon Down in 1866 (Down, 1866), is associated with a number of characteristic features, including characteristic facial features and a number of physical health problems, such as heart defects, thyroid problems and gastrointestinal and immunological disorders.

1.5.2 Aetiology

The most common cause of Down's syndrome is trisomy of Chromosome 21, which accounts for around 95% of cases (Bull et al, 2011). This often arises de novo (i.e. with no previous genetic predisposition) and is caused by a non-dysjunction in meiosis I or II (Ghosh et al, 2009). This is most often a result of a maternal non-dysjunction, and risk increases with increasing maternal age.

The other 5% of cases are translocations or mosaicisms. The most common translocation occurs when the long arm of Chromosome 21 is translocated on to the long arm of Chromosome 14. About 75% of these translocations arise de novo, with the remaining 25% being familial (Bull et al, 2011). In mosaic Down's syndrome, not all cells carry the trisomy. Mosaic Down's syndrome occurs when a trisomy 21 develops in some but not all of the cell lines. Individuals with a mosaicism may have a less characteristic phenotype than those with the full trisomy (Devlin and Morrison, 2004), although this is not always the case (Bull et al, 2011).

Down's syndrome is therefore a syndrome of increased gene dosage rather than caused by faulty or missing genes. The genotype of Down's syndrome is complicated and further research is required to identify which parts of the genotype contribute to specific phenotypic characteristics (Lyle et al, 2009).

1.5.3 Physical characteristics

Down's syndrome is associated with a characteristic facial appearance and a number of physical health conditions. Typical facial features of people with Down's syndrome include oblique eye fissures, epicanthic eye folds, a flat nasal bridge and brachycephaly (a short, broad head) (Jackson et al, 1976). Adults with Down's syndrome are often short in stature and are more likely to be overweight or obese. They also often have hypotonia and a lower blood pressure and pulse rate.

Congenital heart defects are seen in approximately 45% of children born with Down's syndrome (Freeman et al, 1998) and may require surgical correction at a young age. Other conditions associated with Down's syndrome include gastrointestinal and endocrine problems, with 4-18% of people with Down's syndrome having thyroid disease (Murphy et al, 2008; Chen et al, 2007). Other immunological and autoimmune diseases are also common and include susceptibility to infection and skin conditions such as psoriasis. Blood problems associated with Down's syndrome can include polycythaemia in newborns, acute myeloid leukaemia and acute lymphoblastic leukaemia in

children and macrocytosis (Roizen and Patterson, 2003). People with Down's syndrome have high rates of sleep apnoea (Chen et al, 2013), which may go undetected.

People with Down's syndrome are also more likely to have sensory problems: between 38% and 78% may have hearing problems and the prevalence of visual problems increases with age, from 38% in children under 1 year of age to 80% in children aged 5 – 12 years of age (Roizen and Patterson, 2003).

1.5.4 Behavioural phenotype

It is commonly believed that the behavioural phenotype of people with Down's syndrome is that they are friendly and sociable. Although a number of people with Down's syndrome may have these behavioural characteristics, challenging behaviours and mental health problems can also be seen in people with Down's syndrome.

Aside from dementia, mental health problems in people with Down's syndrome are less common than others with intellectual disability (Cooper, 2009a). Mental health problems can include obsessional features, attention deficit and hyperactivity disorder, aggressive behaviour, mood disorders or psychosis. Autism can be a co-morbidity in Down's syndrome, with a frequency that may be as high as 7% (Kent et al, 1999).

Dementia is very common in people with Down's syndrome. Dementia in Down's syndrome usually presents as an Alzheimer's-type dementia and will be discussed in further detail in Section 1.5.

1.5.5 Speech and language

Children with Down's syndrome have delayed speech and language development and speech and language therapy is recommended from an early age. Speech and language problems in people with Down's syndrome

have been well described, and relate to both articulation difficulties and cognitive difficulties. Articulation difficulties are likely to be related to structural features of the tongue and palate (as people with Down's syndrome often have a large tongue in comparison to their small oral cavity) as well as dyspraxia resulting in poor coordination of tongue and palate movements.

Other difficulties include relative weaknesses in phonology, vocal imitation, mean length of utterance and expressive syntax (Pennington et al, 2003). Grammatical difficulties may be explained by a relative weakness in verbal short term memory (Naess et al, 2011), which will be described in further detail in Section 1.4.6.

1.5.6 Cognitive profile

It was previously thought that people with Down's syndrome have a global cognitive impairment, with a proportional reduction in all cognitive skills when compared to those without intellectual disability. More recent research has proven otherwise, and it is now clear that in Down's syndrome, as in many genetic syndromes associated with intellectual disability, the cognitive profile includes relative strengths and weaknesses.

In people with Down's syndrome, as in the general population, the pattern of cognitive skills develops and changes with age. Alongside this, historical changes in the education and welfare systems mean that we need to be cautious when comparing present day cognitive studies in children and adolescents to studies in those who are older adults.

There is a large and growing body of research in the field, much of which focuses on verbal short term memory, which is a relative weakness in people with Down's syndrome (Jarrold and Baddeley, 2001). More recently, research has also examined visual and visuo-spatial memory skills and executive functions.

It has been hypothesised that it may be the late-developing brain regions, including the prefrontal (Edgin, 2013), hippocampal and cerebellar (Nadel, 2003) regions which may be more affected in people with Down's syndrome. In reality, "cognitive functions" are often associated with multiple brain regions and pathways, and a number of areas of the brain may be associated with one specific cognitive skill. Therefore, it is important to remember that the use of neuroanatomical terminology (e.g. "prefrontal skills" or "hippocampal skills") to define cognitive tasks has its limitations, as often multiple brain regions are involved in each specific cognitive task. Specific cognitive skills are also likely to be influenced by a number of different brain functions, such as sight, hearing, attention or concentration.

It can be useful to consider the cognitive profile of people with Down's syndrome in terms of specific cognitive strengths and deficits. A full and detailed description of the cognitive profile of people with Down's syndrome is beyond the scope of this thesis. I will therefore discuss areas of particular interest in relation to my research study. I have used a combination of original references and review articles when describing Down's syndrome in section 1.5. In section 1.6, I will discuss dementia in Down's syndrome in more detail. In this section, which relates more specifically to my research question, I have focussed on using original references.

The cognitive profile of people with Down's syndrome includes weaknesses in the prefrontal, hippocampal and cerebellar domains (Nadel, 2003), with disproportionally smaller brain volume in these areas (Gardiner et al, 2010). The prefrontal cortex plays an important role in executive function and working memory and the hippocampus is important for long term memory. In the remainder of this section, I will summarise the relevant literature on cognitive skills in people with Down' syndrome.

1.5.6.1 Executive function

The prefrontal cortex is involved with executive function. This is a late-developing region, which continues to undergo developmental change into early adulthood (Edgin, 2013). Executive function has been described as "a

set of interrelated control processes involved in the selection, initiation, execution and monitoring of cognition, emotion and behaviour, as well as aspects of motor and sensory functioning" (Roth et al, 2005). Executive function is a complex combination of cognitive skills including initiation, set shifting, response inhibition, working memory, planning and organising and emotional regulation. Impaired executive functioning is seen in people with Down's syndrome, which may be related to the abnormal development of the prefrontal cortex in this population (Rowe et al, 2006). The cerebellum is also thought to play a role in executive function.

Interestingly, Pennington et al found no significant differences on individual measures of executive function between 28 school aged individuals with Down's syndrome (mean age 14.7 years) and 28 mental age matched controls (mean age 4.9 years) (Pennington et al, 2003). The measures used were CANTAB Stockings of Cambridge (a computerised version of the Tower of London task), NEPSY Verbal Fluency, NEPSY Design Fluency, the Stopping task, CANTAB Spatial Working Memory task and the Counting Span task. They demonstrated a correlation of 0.54 between hippocampal and prefrontal composite scores in the Down's syndrome group, when controlling for chronological age, highlighting the fact that, although the two domains are related to different cognitive skills, there is some overlap between them.

Further pilot work from the same research group, however, found that verbal prefrontal tasks might detect differences and it has been suggested that the modality in which information is recalled may moderate the results (Jarrold et al, 2008).

In a later study, the same group found significant differences when comparing 55 individuals with Down's syndrome (from a larger sample of people with Down's syndrome aged 7-38 years old) to 36 mental age matched controls in computer-based tests of set shifting (CANTAB IED) and working memory and inhibitory control (Modified dots task, combined phase) (Edgin et al, 2010a). The CANTAB IED task and Modified dots task are

largely non-verbal tasks (ie. they do not require verbal responses), and this difference is therefore not explained by a verbal modality. It is not clear why these tests showed a significant difference between individuals with Down's syndrome and mental age matched controls, when no differences were found in the previous study. This may be due to differences in sample size, differences in the ages of participants or, perhaps because the prefrontal tests used in Edgin's 2010 study were more sensitive.

Studies have demonstrated specific deficits in working memory and set shifting in children and adults with Down's syndrome. Lanfranchi et al demonstrated that 15 adolescents with Down's syndrome performed at a significantly lower level when compared to 15 mental age matched typically developing children on tasks assessing set shifting, planning/problem-solving, working memory and inhibition/perseveration but not on the tasks assessing verbal fluency (Lanfranchi et al, 2010).

Rowe et al found that 26 adults with Down's syndrome (mean age 33.35 years) performed at a significantly lower level on a number of tests that assessed executive function compared to 26 age matched participants with intellectual disability who did not have Down's syndrome (Rowe et al, 2006). After correcting for multiple comparisons, a significant group effect remained for the Weigl Colour-Form Sort Test (a test of set shifting), Attention Sustained (a test of attention) and Raven's Coloured Progressive Matrices (used to assess non-verbal reasoning ability).

1.5.6.1.1 Working memory

Working memory refers to short term memory, where "information is actively held 'online' so that it may be manipulated and transformed in the service of planning and guiding cognition and behaviour" (Roth et al, 2005). I will therefore use the terms working memory and short term memory synonymously in this thesis.

Baddeley proposed abandoning the concept of a single unitary short term memory in favour of a working memory model. His working memory model

included a central executive and two temporary storage systems: a phonological loop (related to verbal short term memory) and a visuo-spatial sketchpad (related to visuo-spatial short term memory) (Baddeley and Hitch, 1974; Baddeley, 1986). The phonological loop processes verbal information using a process of rehearsing phonological sounds (words) and the visuo-spatial sketchpad processes memories through visual imagery. This model was later revised to include an episodic buffer, which integrates information from the subsidiary systems and long term memory into a single episodic representation (Baddeley, 2000). It is thought that the central executive component of working memory relies on the prefrontal cortex (Edgin et al, 2010b).

There is a large body of research that has examined verbal short term memory in people with Down's syndrome (Laws, 2002; Jarrold et al, 2002; Jarrold et al, 2008). In summary, this has shown that verbal short term memory in people with Down's syndrome is a relative weakness and it has been hypothesised that deficits in verbal short term memory may lead to the comparatively weaker verbal abilities seen in people with Down's syndrome, although this is an area that requires further research (Jarrold et al, 2008).

Other studies have also looked at visuo-spatial working memory in people with Down's syndrome. Lanfranchi et al found that there was a dual task deficit when assessing 45 children with Down's syndrome and 45 verbal mental age matched children (Lanfranchi, 2012). They found impairments in the Down's syndrome group in verbal tasks and further impairment in all dual-task (verbal and visuo-spatial working memory task) conditions.

Visu-Petra et al administered 5 CANTAB visuo-spatial tasks to 25 children with Down's syndrome and 25 mental age matched controls (Visu-Petra et al, 2007). They did not find support for a visual versus spatial dissociation in recognition memory and concluded that performance impairment in the visuo-spatial domain parallels the increase in working memory.

1.5.6.2 Long Term Memory

Long term memory has been described as memory for storage of material that is not kept active. It can be divided into implicit memory (non-conscious knowledge and learning) and explicit memory (consciously recollected memory for facts and events) (Jarrold, 2008). The hippocampus is important for explicit memory, and is involved in consolidating networks for long-term retrieval of information (Edgin et al, 2010b). Different theories propose different main functions of the hippocampus. In the Cognitive Map Theory, the hippocampus is thought to be specialised to process spatial information (O'Keefe and Nadel, 1978). However, the Relational Theory (Cohen and Eichenbaum, 1993) and Declarative Theory (Squire, 1986) suggest that the hippocampus has more general processing mechanisms and is important in the development of both spatial and semantic memory (Edgin et al, 2010b).

A number of the studies examining explicit long term memory in people with Down's syndrome have studied memory for verbal rather than visuo-spatial information (Jarrold et al, 2008).

Carlesimo et al investigated long term memory in 15 people with Down's syndrome (mean age 16.7 years) and compared them to 15 people with other intellectual disability (mean age 17.1 years) and 30 mental age matched children. They used tests of verbal and visuo-perceptual explicit memory and a verbal repetition priming task and found that people with Down's syndrome performed the poorest in the tests for explicit memory and had a particular difficulty in organising verbal material (Carlesimo et al, 1996).

In a study by Vicari et al, 15 participants with Down's syndrome (mean age 16 years, 5 months) were found to have typical learning of visuo-spatial sequences but impaired learning of visuo-object patterns compared against a mental age matched control group (Vicari et al, 2005). This was in contrast to participants with Williams syndrome (another genetic syndrome associated with intellectual disability and often studied in comparison to people with Down's syndrome), who displayed a different profile. This finding highlights

that visuo-object and visuo-spatial processes are likely to be mediated by different neural networks.

As previously reported, a number of studies from the Down Syndrome Research Group, based in the USA (the group that published the Arizona Cognitive Test Battery), have examined cognition, including long term memory in people with Down's syndrome (Pennington et al, 2003; Edgin et al, 2010a). Alongside findings on prefrontal skills, as reported above, Pennington et al identified poorer performance in participants with Down's syndrome compared to mental age matched controls in all the hippocampal measures evaluated (NEPSY list learning, Morris water maze, CANTAB Pattern Recognition and CANTAB Paired Associates Learning (PAL)) (Pennington et al, 2003).

In another study from the same research group, comparing adolescents and young adults with Down's syndrome (n=27) or Williams Syndrome (n=28) and closely matched chronological age and IQ matched controls, different patterns of strengths and weaknesses in memory were identified, with verbal immediate memory (digit span) being most related to variation in IQ and spatial associative memory (CANTAB PAL) being related to adaptive behaviour in the Down's syndrome group (Edgin et al, 2010b).

In a separate study, a significant difference was found when the number of CANTAB PAL first trials correct (a measure of spatial associative memory) was compared between a group with Down's syndrome (n=55) and a mental age matched control group (n=36). No significant difference was seen in the Computer-generated arena task (a measure of spatial memory) based on the Morris Water Maze (Edgin et al, 2010a).

1.5.6.3 Cerebellar functions

The cerebellum is well known for its role in motor functions, including coordination and balance. However, in recent years, it has become acknowledged that the cerebellum also has a role in cognition. This is yet to

be fully understood, but it is hypothesised that the cerebellum's role in mental functions parallels its role in motor functions, forming an internal model through repeated performance and feedback (Buckner, 2013).

A recent systematic review of PET and fMRI studies and cognition has identified some of the main cognitive functions of the cerebellum. These include executive function, working memory, emotion, language and music and timing (Keren-Happuch et al, 2012).

People with Down's syndrome have smaller cerebellar volumes (Pinter et al, 2001). This may be related to the fine movement and gait problems that are also often seen in people with Down's syndrome.

A study in human foetuses with Down's syndrome at 17-21 weeks gestation found that the cerebellum had an immature pattern, reduced volume and fewer cells in all cerebellar layers. The authors suggest that in foetuses, the reduction in cerebellar cells results from a reduction in cell proliferation rather than increased cell death (Guidi et al, 2011).

Interestingly, studies in mice have shown that the cerebellar morphology can be normalised by using SAG, an agonist of the Sonic Hedgehog pathway (a pathway that is known to have a role in early development), administered at birth. Although this normalises cerebellar morphology and restores the ability to learn a spatial navigation task (likely to be mediated by the hippocampus) (Das et al, 2013), it has not been shown to restore cerebellum dependant motor learning deficits (Gutierrez-Castellanos et al, 2013).

There is a large body of research on movement in people with Down's syndrome, although the research specifically on cerebellar function itself is limited. People with Down's syndrome have longer reaction times, movement times and greater movement errors in single limb, single target movements when compared to typically developing controls. These are thought to be related to both central as well as peripheral processes. (Lawrence et al, 2013).

Research on cerebellar cognitive functions in people with Down's syndrome is very limited. In Edgin's recent study, a significant difference in cerebellar tasks between the Down's syndrome group and mental age matched controls was seen in one of the three cerebellar tasks administered (participants with Down's syndrome had a longer mean latency in in the tabletop finger sequencing task, but there was no significant difference between the two groups in CANTAB SRT or NEPSY visuomotor precision) (Edgin et al, 2010a).

There is a need for a further understanding of the cerebellum's role in cognition. Following this, further studies are then required to examine cerebellar cognitive skills in people with Down's syndrome.

1.5.6.4 Cognitive profile over time

Patterson et al have recently reviewed the longitudinal studies looking at cognitive development across childhood in Down's syndrome (Patterson et al, 2013). They found that all 6 studies that measured general IQ reported a decline in IQ over time. Of the 7 studies that measured specific cognitive domains, all 7 studied language and memory and 4 studies assessed visuo-spatial skills. There was an increase in most of the test raw scores over time, and an increase in age-equivalent scores, although this was substantially slower than the rate of increase in chronological age of participants. Tests assessing receptive language and word recognition were more likely to improve than those testing phonological skill and short term memory. The authors concluded that cognitive trajectories in children and adolescents with Down's syndrome cannot be clearly defined using current published data.

I have not detailed all the studies included in this review, as they review studies in children and my research question relates to older adults. However, one of the studies that was included in the review paper has published further data on participants aged up to 45 years (data up until age 21 was included in the review). This study examined cognitive function in a community sample of people with Down's syndrome and found that there

were no statistically significant differences in cognitive functions (including intelligence, language, reading, arithmetic and daily living skills) from age 21 and/or 30 compared to the same individuals at age 35 (Carr J, 2003). In a further follow up of this sample, apart from two participants with a diagnosis of dementia, mean IQs (verbal and non-verbal) changed very little from age 21 to age 45. However, scores on memory tests (Oliver and Crayton's dementia battery and Rivermead Behavioural Memory Test for Children) had declined, in some cases significantly. The author suggests that this may indicate that other members of the cohort may be showing early signs of dementia (Carr J, 2012).

Dementia and subsequent decline in cognitive functions most commonly presents when people with Down's syndrome are in their 50s, but can present earlier in some individuals. Dementia will be discussed later on in this chapter.

An MRI study of adults with Down's syndrome found that although cerebellar volumes were disproportionately small in adults with Down's syndrome compared to controls, they did not reduce significantly with age any more than the control group. The authors concluded that cerebellar volume did not appear to be responsible for the age related decline in fine motor control seen in people with Down's syndrome (Aylward et al, 1997).

1.5.6.5 Summary

There has been extensive research looking at the cognitive profile of people with Down's syndrome. The research indicates that people with Down's syndrome have relative weaknesses in some aspects of executive function and memory, in particular, verbal short term memory. There is some evidence that they may have impairments in cerebellar cognitive function, but there is a need for further research in this area.

In childhood, IQ has been shown to decline over time. In younger adulthood, it may be that IQ remains fairly stable, until some people present with the cognitive decline associated with dementia in Down's syndrome.

Although cognition in Down's syndrome is a large and rapidly growing research field, it is often difficult to compare studies, as many studies use different cognitive tests in different populations and with different age groups. Some studies use mental age matched controls, others use chronological age matched controls and others use controls from the intellectual disability population (including controls with no genetic diagnosis and controls with other genetic syndromes, such as Williams syndrome). These have their individual advantages and disadvantages: studies which use mental age matched controls use a control group of comparable mental age but controls are often at a much younger chronological age and have therefore had less life experience to allow for the learning or development of certain skills, such as motor or computer based skills. The reverse is true for studies that use chronological age matched controls and for this reason, chronological age matched controls are less commonly used in more recent studies. Studies which use controls from the intellectual disability population may be limited by a number of factors, including the heterogeneity of the population and the specific cognitive differences known to be found in people with some genetic syndromes.

Studies that use cognitive assessment batteries are likely to require multiple analyses and there is a danger of generating type I errors (ie. false positive results) and/or that negative findings are not reported. Very few of the studies report a power calculation and it is therefore difficult to determine whether analyses may be likely to generate any type II errors (ie. false negative results). While it is important to bear these limitations in mind when considering the research in this area, it is also important to acknowledge the contribution that research on cognition in people with Down's syndrome has made to our understanding of cognition and cognitive deficits in people with Down's syndrome, in people with intellectual disability and in the general population.

1.6 Dementia in Down's syndrome

Dementia is characterised by a decline from baseline functioning in memory and other cognitive and daily living skills. In ICD-10, a decline in emotional control, motivation or social behaviour is also required for a diagnosis (World Health Organisation, 1992).

The definition of dementia is given in the international classification systems, ICD-10 (World Health Organisation, 1992) and DSM-IV (American Psychiatric Association, 2000). In order to make a diagnosis, both classification systems require development of a decline in memory and other cognitive functions. DC-LD is a diagnostic classification system based on ICD-10, and designed for use in adults with moderate to profound intellectual disability (Royal College of Psychiatrists, 2001). It emphasizes the importance of a change from a baseline level of functioning

In DSM 5, dementia is found in the category of Major Neurocognitive Disorder (American Psychiatric Association, 2013). One of the main differences between DSM 5 compared to DSM-IV and ICD-10 is that although a decline in cognitive skills is required for a diagnosis, this does not necessarily need to include a decline in learning and memory. Other cognitive skills that may be seen to decline in the DSM 5 diagnosis include complex attention, executive function, language, perceptual-motor and social cognition. It also specifies that diagnosis should be based on informant report and an impairment in cognitive performance, ideally measured through standardised neuropsychological testing. This highlights the importance of assessing a range of cognitive skills, including, but not limited to memory, and using neuropsychological testing as well as informant report when assessing for a diagnosis of dementia. It remains to be seen how the revised editions of ICD (due to be revised in 2015) and the recently revised DSM 5 diagnostic criteria will affect the diagnosis of dementia in people with intellectual disabilities.

Alzheimer's disease is a type of dementia which can present insidiously with a decline in memory, with subsequent gradual deterioration of brain functions, including decline in other cognitive skills. It is the most common type of dementia both in the general population and amongst people with intellectual disability.

Pathological features of Alzheimer's disease include amyloid plaques and neurofibrillary tangles in the brain The amyloid cascade hypothesis suggests that amyloid deposits are causative of Alzheimer's pathology, leading to neurofibrillary tangles, vascular damage, neuronal cell loss and dementia (Hardy and Higgins, 1992), although this hypothesis continues to be revised and challenged (Ballard et al, 2011).

Mutations in genes related to the production of amyloid, including Presenilin 1 and Presenilin 2 and Amyloid Precursor Protein (APP) are associated with early onset, autosomal Alzheimer's disease (Hardy, 1997). Genome-wide association studies (GWAS) have suggested several new genes associated with Alzheimer's disease (Harold et al, 2009).

Other types of dementia include vascular dementia, Lewy-body dementia, Fronto-temporal dementias as well as dementias due to other conditions such as dementia in HIV or dementia in Parkinson's disease. In the general population, mixed patterns of dementia (for example, mixed Alzheimer's disease and vascular dementia) are common.

Over the past few decades, with improvements in the life expectancy of people with Down's syndrome, it has become more evident that one of the behavioural phenotypes of Down's syndrome is the increased risk of developing dementia of Alzheimer's type (DAT).

1.6.1 Neuropathology

1.6.1.1 Genetics

At present, the most accepted hypothesis as to why people with Down's syndrome are at greater risk of developing dementia of Alzheimer's type is that it is related to the Amyloid Precursor Protein (APP) gene. Amyloid Precursor Protein (APP) is one of the proteins associated with the production of amyloid. The gene that codes for APP is located on chromosome 21 and is therefore triplicated in people with Down's syndrome, resulting in an overexpression of APP. It has been shown that the number of trinucleotide repeat alleles in APP can influence the age of onset of dementia in Down's syndrome (Margallo-Lana et al, 2004)

Several other genes on chromosome 21 are also may potentially be related to the development of dementia of Alzheimer's type in people with Down's syndrome. This may include β-site APP cleaving enzyme-2 (BACE-2), which has been shown to affect age of onset of dementia (Mok et al, 2014) and DYRK1A (Park et al, 2009)

There has also recently been increased interest in other genes that may play a cumulative role in predisposing to dementia, both in the general population and in people with Down's syndrome. The variant of gene apolipoprotein E (APO-E) allele 4 is known to be associated with an increased risk of developing Alzheimer's disease in the general population (Ballard et al, 2011). APO-E has also been shown to influence the development and progression of dementia of Alzheimer's type in people with Down syndrome (Prasher et al, 2008).

A recent study has identified associations with the age of onset of Alzheimer's disease in people with Down's syndrome with PICALM and the APO-E loci (Jones et al, 2013). Further genome-wide association studies (GWAS) are likely to increase our understanding of genetic factors in dementia in people with Down's syndrome.

1.6.1.2 Brain Pathology

In older adults with Down's syndrome without dementia, changes in medial temporal lobe volume have been shown to occur with age and to be related to memory (Krausky et al, 2002). This can make it difficult to determine dementia in people with Down's syndrome through brain scans, as brain atrophy is a feature of Alzheimer's disease and early changes may be seen in the medial temporal lobes (Tartaglia et al, 2011).

Potential dementia indicators (using the carer rated DLD questionnaire) in people with Down's syndrome have been shown to be correlated with both structural and functional brain changes (including the combination of decreased grey matter volume and increased cerebral glucose metabolic rate in parts of the brain, including the parahippocampus/hippocampus and frontal lobe) (Haier et al, 2008).

Alzheimer's pathology is thought to be present in the brains of virtually all people with Down's syndrome aged 40 and over (Head & Lott, 2004), although not all adults with Down's syndrome develop the symptoms of dementia. Previous research has shown that a diagnosis of dementia in people with Down's syndrome is more closely related to the density of neurofibrillary tangles rather than the density of amyloid plaques (Margallo-Lana et al, 2007).

1.6.1.3 Other Factors

There are a number of factors that may play a role in influencing the presentation of dementia in people with intellectual disability. Comorbidities, such as epilepsy, which is more prevalent in people with intellectual disability (McGrother et al, 2006), may influence the presentation. Also, people with intellectual disabilities may have a lower cognitive reserve due to lower baseline cognitive function. This may lead to earlier development of symptoms during the course of dementia, as low cognitive reserve is rapidly overcome by the disease (Strydom and Sinai, 2014).

Important modifiable risk factors for Alzheimer's disease can include factors such as obesity, smoking, physical activity and alcohol intake (Ballard et al, 2011). Some of these risk factors may be more common in people with Down's syndrome, including obesity (de Winter et al, 2012) which may be related to genetic factors as well as reduced exercise, poorer awareness of healthy eating and certain medications.

The specific protective factors in those people with Down's syndrome who do not develop the clinical features of dementia are still not fully understood, and risk is likely to be related to a combination of factors, including genetic and environmental factors.

Improved understanding of the neurobiology of Down's syndrome is now leading to consideration of potential treatment options for improving cognitive functioning or modifying the dementia process in people with Down's syndrome. Several successful mouse model studies have led to several trials in humans (Costa and Scott-McKean, 2013), including a recent trial of memantine in people with Down's syndrome (Hanney et al, 2012).

1.6.2 Epidemiology

Dementia in Down's syndrome presents at a younger age and at a higher rate than the general population (see Sinai et al, 2014 for a review). The prevalence of dementia in adults with Down's syndrome aged between 40 and 49 has been found to range from approximately 6% to approximately 10% (Tyrrell et al, 2001; Holland et al, 1998). Between 50 and 59 years of age, 30 - 40% of people with Down's syndrome have been estimated to have a diagnosis of dementia (Tyrrell et al, 2001; Holland et al, 1998), and estimates in those aged 60 and older range from 26% to 77% (Coppus et al, 2006; Visser et al, 1997). Prevalence rates of dementia in people with Down's syndrome are considerably higher than the prevalence of Alzheimer's disease in people with intellectual disability aged 60 and over who do not have Down's syndrome, which has been estimated at around 8.6% (Strydom et al, 2007). Incidence of dementia in people with Down's syndrome has

been shown to increase with age, and incidence in those aged 60 and older has been found to be 13.3 per 100 person years (Coppus et al, 2006).

Unlike Alzheimer's disease in the general population, in which female gender is associated with an increased risk of Alzheimer's disease (Launer et al, 1999), risk of dementia in people with Down's syndrome has not been found to be associated with gender. However, the age at onset of dementia in women with Down's syndrome has been shown to be correlated with the age of onset of menopause, with earlier onset of dementia associated with earlier menopause (Cosgrave et al, 1999).

One follow up study in an institutionalised sample of people with Down's syndrome found that the median age of onset of dementia was 55.5 years, with a mean age at death of 59.3 years (Margallo-Lana et al., 2007). A recent survival analysis of a community sample found that survival from diagnosis of dementia to death was approximately 5 years (Mockryz C et al, personal communication), which is comparable to survival rates from time of diagnosis in the general population, although age at diagnosis in the Down's syndrome population is much lower than in the general population.

1.6.3 Cognitive profile

Like the general population, memory changes are an important symptom in dementia in people with Down's syndrome. Although there are differences in the clinical presentation of dementia in people with Down's syndrome, it is generally accepted that the type of dementia that is commonly seen in people with Down's syndrome is dementia of Alzheimer's type.

Older adults with Down's syndrome have been shown to perform more poorly on cognitive tests, particularly those requiring planning and attention, when compared to younger adults with Down's syndrome and both older and younger adults with non-Down's syndrome intellectual disability (Das et al, 1995).

Adams and Oliver studied 30 adults with Down's syndrome at three time points over 16 months. Ten participants showed cognitive deterioration during this time. The group with cognitive deterioration showed decreases on measures of executive function and significant changes in behaviour during the course of the study, which were not just due to memory decline. The study showed that in the stages before a diagnosis of dementia, adults with Down's syndrome have an increased frequency of behavioural excesses and deficits (Adams and Oliver, 2010).

Although forgetfulness and confusion are common early symptoms, frontal lobe related features, including diminished initiative and social withdrawal also present early in dementia in people with Down's syndrome (Deb et al, 2007). In this qualitative study, Deb et al also noted a general slowness, including slowness in activities and speech.

These two studies draw attention to early frontal lobe related features in dementia in people with Down's syndrome and go some way to supporting Ball et al's finding that adults with Down's syndrome may meet the criteria for a dementia of frontal type before they progress to meeting the criteria for Alzheimer's disease (Ball et al, 2006a). When a group of older adults were assessed using six executive function tests and six memory measures, Ball et al found that the group with dementia of Alzheimer's type (DAT) (n=25) showed impaired performance on all measures compared to the non-DAT group (n=78) (Ball et al, 2008). In a further analysis on the non-DAT group, they found that disinhibited behaviours were more commonly reported by carers than apathy or executive dysfunction and proposed that the biological basis for this may be through the serotonergically mediated orbito-frontal circuit (Ball et al, 2010).

Cognitive functions have been shown to decline sequentially, with different cognitive functions being affected at different stages of the dementia. Those with "questionable" dementia, as well as having memory loss, have demonstrated declines in block design and coding subsets, those at an "early" stage show the previous declines, as well as declines in object

assembly, picture completion (visuo-spatial organisation), arithmetic and comprehension (working memory) and those in the "middle" stage of dementia show the previous declines as well as declines in information, vocabulary (sematic memory) and digit span (short term memory) (Devenny et al, 2000).

In a longitudinal study in the USA, Krinsky-McHale et al (2002) showed that 14 participants with early stage dementia of Alzheimer's type and Down's syndrome showed severely diminished verbal long term storage and retrieval processing abilities compared to the group of 71 participants without a diagnosis of dementia.

1.6.4 Other clinical features

When behavioural and emotional changes in people with Down's syndrome and dementia were compared with a group of people with Alzheimer's disease from the general population, the group with Down's syndrome were more physically active, although they had fewer behavioural problems and delusions (Temple and Konstantareas, 2005).

The later stages of dementia in Down's syndrome are often associated with mobility issues and falls, and myoclonic jerks and epilepsy. The frequency of myoclonic jerks and epilepsy in Down's syndrome and dementia is much higher than in the general population. A recent longitudinal study reported epilepsy in 74% of participants with Down's syndrome and dementia and noted that the onset of epilepsy was often within the same time period as dementia decline (McCarron et al, 2014).

End stage dementia in people with Down's syndrome can present with similar symptoms to end stage dementia in the general population and can include severe memory impairment, changes in personality and affect as well as incontinence, immobility and a complete loss of self care skills (Prasher, 1995).

1.6.5 Summary

Dementia in older adults with Down's syndrome is common, although estimates of prevalence rates vary. Dementia typically presents at around age 55, which is much younger than dementia in the general population. Although there are differences in the clinical presentation of dementia in people with Down's syndrome, including early presentation of frontal lobe related features and an increased rate of epilepsy, it is generally accepted that the type of dementia that is commonly seen in people with Down's syndrome is dementia of Alzheimer's type.

1.7 Measuring cognitive deficits in people with Down's syndrome

There are several assessment tools that can be used for assessing cognitive skills and/or dementia in people with intellectual disability, as demonstrated by the extensive literature in the area. Most tests require assessments at repeated intervals in order to assess change from baseline functioning. There is some overlap between those tools that assess for dementia and those that assess cognitive function.

Measurement of cognitive deficits in people with Down's syndrome can be challenging. Several factors can influence performance, including sensory deficits, particularly hearing and visual problems. Attention, concentration and verbal abilities can also affect performance. Alongside verbal abilities, the language of the participant and language that the tests are administered in will affect performance and it is important to note that most of the tests are designed by and for use in Western countries, where English is the first language. Alongside this, differences in American English and British English may require slight alterations in instruction manuals.

As previously mentioned, a participant's educational and past social history may affect performance, particularly when considering the differences in health and education systems over the past 50 years and when comparing

opportunities given to those brought up in a family environment compared to those brought up in an institution. Other factors that may influence assessment are the environment the assessment is conducted in – including location, familiarity, any distractions and who the participant is supported by.

A particular issue for cognitive assessments in people with Down's syndrome is their relatively poor verbal abilities, which may act as a confounder in tests that require verbal responses.

A recent systematic review has compiled a list of assessment instruments for dementia in Down's syndrome (Zeilinger et al, 2013). The authors identified 114 different instruments, including 79 instruments involving the person with Down's syndrome and 35 informant rated assessments. They also identified 4 test batteries. They highlighted that despite the variety of tools, there is currently no consensus on how best to assess dementia in this population and suggested that a consensus approach or instrument would be valuable for research and clinical practice.

See Table 1.1 for some of the common screening and assessment tools that can be used when assessing dementia in people with intellectual disability.

Table 1.1 – Some tools used to assess dementia in people with intellectual disability – adapted from British Psychological Society and Royal College of Psychiatrists, 2009 (Strydom and Sinai, 2014)

Informant rated tools
Dementia Questionnaire for people with Learning Disabilities, DLD (Evenhuis et al, 2007)
Dementia Screening Questionnaire for Individuals with Intellectual Disabilities, DSQUIID (Deb et al, 2007b)
Adaptive Behaviour Dementia Questionnaire, ABDQ (Prasher et al, 2004)
CAMDEX-DS informant interview (Ball et al, 2006b)
Assessments of daily living skills and functioning
Assessment of Motor and Process Skills (AMPS) (Fisher, 2006)
AAMD Adapted Behaviour Scales (ABS) (Nihira et al, 1974)
Adaptive Behaviour Assessment System-II (ABAS-II) (Harrison and Oakland, 2003)
Vineland Adaptive Behaviour Scales: Second edition (Sparrow et al, 2007)
Test Batteries
CAMCOG-DS (Ball et al. 2006b)
Neuropsychological Assessment of Dementia in Adults with Intellectual Disabilities (NAID) (Crayton et al, 1998)
Severe Impairment Battery (Saxton et al, 1993)
Test Battery for Dementia (Burt and Aylward, 2000)

1.7.1 The Arizona Cognitive Test Battery (ACTB)

The Arizona Cognitive Test Battery (ACTB) has been developed in the USA to assess cognitive function in detail in people with Down's syndrome. It assesses three specific brain areas that are known to be associated with cognitive difficulties in people with Down's syndrome; the prefrontal, hippocampal and cerebellar areas (Edgin et al, 2010a). It has been validated for use in both lab and home environments and is designed to assess non-verbal responses, in order to reduce the fact that poor verbal ability may confound results. In an attempt to overcome potentially high floor levels in this population, several of the tasks include measurements of errors as well as measures of success.

It has been validated amongst children and adults with Down's syndrome, up until the age of 35. It has not been validated in older adults with Down's syndrome, and it is not known if the battery would be of value in assessing for dementia and whether it can distinguish between older adults with and without dementia of Alzheimer's type.

Validation of this test battery in older adults with Down's syndrome is important, given the high risk of dementia in this group. Furthermore, the psychometric properties and floor effects of the ACTB need to be confirmed in an older population as it may differ compared to younger adults due to known changes in cognitive skills, as described previously, as well as additional morbidity such as vision and hearing problems.

With the recent trials for cognitive enhancers for those with intellectual disability associated with specific syndromes (Kuehn, 2011) and advances in pharmacological treatments for Alzheimer's disease, there is an increased need to obtain acceptable, validated and standardised neuropsychological measures of cognitive function in people with Down's syndrome. Neuropsychological measures of cognitive function can also help clarify a diagnosis of dementia, and are more likely to be used in the future, both clinically and in research, as the emphasis in the diagnosis of dementia

moves away from a condition of memory loss to that of a neurocognitive disorder, which may feature a variety of cognitive deficits.

It has been proposed that the ACTB could be used to measure outcomes in cognitive and dementia treatment trials in this population. It is hoped that this will help to target management and evaluate treatment efficacy more specifically.

A further understanding of dementia in people with Down's syndrome may, in turn, lead to a better understanding of dementia in the general population, and may go on to improve management of the increasing population that is affected by this disease.

1.8 Summary

The life expectancy of people with Down's syndrome is increasing, with more people now living into their 60s and 70s. Over recent years, it has become more evident that people with Down's syndrome are at increased risk of dementia. Alongside this, people with Down's syndrome have specific cognitive deficits, including relative weaknesses in some aspects of executive function and verbal memory. The Arizona Cognitive Test Battery (ACTB) has been developed to assess prefrontal, hippocampal and cerebellar cognitive deficits in people with Down's syndrome. It has been proposed that the ACTB could be used to measure outcomes in cognitive enhancer and dementia treatment trials in this population. It has not yet been validated in older adults with Down's syndrome.

Chapter 2. Methods

Chapter 2. Methods

2.1 Overview

In this chapter, I will first describe the aims of the study. I will then discuss specific ethical issues regarding capacity and consent relating to this study before describing the sample and setting of the study. Following this, I will detail the study procedures and the cognitive tasks used in this study. I will end by describing my analysis plan.

2.2 Aim

To assess the use of the ACTB in older adults with Down's syndrome and establish its validity in identifying the changes associated with dementia.

2.3 Hypotheses

2.3.1 Primary Hypothesis

The ACTB is able to detect differences between people with Down's syndrome who have early stage dementia and those who do not have dementia.

2.3.2 Secondary Hypotheses

- There are specific differences in the neuropsychological profiles of people with Down's syndrome who have dementia and those who do not have dementia. These include differences in:
  - Prefrontal
  - Hippocampal
  - Cerebellar areas

- The ACTB is a valid test battery for use in older adults with Down's syndrome.
  - It has acceptable floor and ceiling effects (i.e. similar to table top tests)
  - It has good concurrent validity when compared to traditional table top tests tapping into the same or similar brain functions
  - It has good concurrent validity when compared to informant ratings tapping into the same or similar brain functions

2.4 Ethics

The study was approved by the North Wales – West Research Ethics Committee. NHS Research and Development and local NHS site permissions were also granted.

The assessment battery and carer rated questionnaires represented a compromise between the desire, on the one hand, to obtain as much useful and relevant information as possible to answer the research question and on the other, to avoid long and tiresome assessments for the participant and their carers or relatives.

At the request of the Research Ethics Committee, if a participant who had not been diagnosed with dementia by their care team presented with symptoms suggestive of dementia on the cognitive assessment, the care team was informed, in order to take the appropriate action.

2.4.1 Capacity and Consent

This study included participants who lacked capacity. I believed that it was important that people who lacked capacity were included in this study. This ensured that the data collected was relevant and generalisable to this population. It also allowed people with Down's syndrome who may lack capacity to be included in research that may lead to improvements for them and others with Down's syndrome and dementia.

The study was conducted in accordance with the Mental Capacity Act (Department for Constitutional Affairs, 2005). The Mental Capacity Act has clear specifications about research with participants who may lack capacity. This includes identifying a consultee in cases where participants lack capacity to consent. It also stipulates that the research must be connected to the impairment that causes the lack of capacity and that the research would not be as effective if only those with capacity to consent were to participate.

In this study, both Down's syndrome and/or dementia may result in lack of capacity to consent to the study.

In order to aid understanding, the study information sheet and consent forms were developed in consultation with an accessible information officer (RL) and designed to be as accessible as possible for people with intellectual disabilities.

In cases where a participant lacked capacity to consent, the decision was discussed with the participant as well as with a consultee. A personal consultee was approached in the first instance if possible or practical. If there was no personal consultee available, I identified a suitable nominated consultee, who was not involved in the study, as per the Mental Capacity Act. This was often a paid carer, or manager of the home or day centre.

The consultee was given information about the role of a consultee in research, as well as an information sheet about the research and given the opportunity to ask questions.

Participants (or their consultee, if the participant lacked capacity) could ask to withdraw at any time. The assessment was stopped if the participant, consultee, research or care team identified consistent signs that the participant was no longer happy to continue in the study.

2.5 Setting

The study was conducted in the Greater London area and surrounding counties. This is an area with a diverse population, including a large range of ethnic and socio-economic backgrounds, as well as having a variety of different types of accommodation for people with intellectual disabilities.

There are a number of different services that support people with intellectual disabilities, including people with Down's syndrome, living in London. These include community intellectual disability services, which are often integrated

health and social services teams, and specialised inpatient services. These services were approached and invited to nominate participants.

2.6 Sample

Participants were resident in the Greater London area or surrounding counties.

Health professionals of community intellectual disability teams and one specialist inpatient service were asked to approach service users with Down's syndrome. Several intellectual disability teams had a local database of people with Down's syndrome who they support.

Once participants were identified, the intellectual disability teams invited potential participants to join the study. An information sheet, with contact details for how to join the study was given to or posted to participants and their carers. The referring team passed on details of potential participants who agreed to find out more about the study to the research team.

As recruitment through these channels was slow, I also approached local care homes or day centres to recruit participants.

If the participant or their consultee agreed to participate in the study, I liaised with service users and their caregivers and arranged a time for the assessment. Assessments were conducted at a convenient place for participants; this was often at their home, a relative's home or their day centre.

2.6.1 Sample size calculation

The sample size was calculated in consultation with a statistician (KR) using Sample Size Tables for Clinical Studies software (Machin et al, 2009). The calculation assumed that CANTAB PAL first trial memory score is normally distributed with a standard deviation of 6.01 (based on previous research,

Edgin et al, 2010a). To detect an effect size of 0.74, at 80% power and with a 5% overall significance level, it was calculated that a total of 60 participants (30 participants in each group) (68 if adjusted for a 10% dropout) would be required.

2.7 Exclusion and inclusion criteria

I used broad inclusion criteria in order to provide as generalisable a sample as possible and to maximise the sample size.

2.7.1 Inclusion criteria

- Men or women with a clinical diagnosis of Down's syndrome
- Aged 45 or over

I included people on psychotropic medication, including those on cholinesterase inhibitors or memantine.

Participants were required to be able to understand simple verbal commands and attempt simple puzzles and games.

2.7.2 Exclusion criteria

- Active medical problems, including untreated thyroid problems or epilepsy. (Participants with stable and treated medical problems were included.)
- Active psychosis or affective disorder (Participants with stable and treated mental health problems were included.)
- Previous CVA (Cerebrovascular Accident) or significant head injury

Participants with sensory impairments that did not prevent them from being able to participate in the tasks were included. Participants with sensory impairments that prevented them from being able to participate in the tasks were not included.

2.8 Study procedures

After obtaining consent from the participant or their consultee, the individual was entered into the study.

I met with participants and collected the data in one session if possible. However I took a flexible approach to this and at times data were collected over two or three sessions. Participants were offered a break half way through the assessment, or more as required. At the end of the assessment, participants were given a choice of a small gift (such as a sticker book, a colouring book or a CD) or a £10 gift voucher.

Relatives or carers were asked to be present during the meeting and were asked to complete informant questionnaires while the participant completed the cognitive tests. On most occasions, this person was also the consultee. Where relevant, they were reminded not to guide the participant in completing the tests, but at times carers were able to offer helpful suggestions on how to engage participants or how to best communicate the instructions to participants.

The data collection form was completed from verbal information given by the participant or informant in the first instance. Where applicable, specific variables were then cross-checked with the participant's care team and/or medical records.

A summary of findings was sent to the participant, the participant's General Practitioner (GP) and their community intellectual disability team, where relevant, after the assessment.

2.8.1 Feasibility and pilot study

An assessment manual was developed by adapting the ACTB manual (Edgin, 2012) and selected clinical table top assessments. Table top assessments were selected by identifying tests that assessed pre-frontal, hippocampal and cerebellar functions and were used either in research or clinically. Consideration was also given to the feasibility of the task. As very little is currently understood on cerebellar cognitive functions, and there are no widely used tests which specifically assess cognitive cerebellar function, motor cerebellar tests were used to assess cerebellar function.

Where appropriate, I amended the wording of some of the assessments from American English and to more simple English. For example, in the CANTAB IED, when asking participants to identify the rule, I amended the term "correct" to "right".

The assessment was subsequently piloted on the first 3 participants. Following this, an additional teaching task, the CANTAB MOT task, was added to the computer tasks.

2.8.2 Revision of study procedures

A further revision was made half way through recruitment, where the virtual computer generated Arena task was taken out of the assessment battery. This was due to inaccuracies in screen resolution, leading to poorly identifiable visual cues that were essential for validity of the task.

Half way through recruitment, the order of the tasks was counter-balanced, to reduce the potential effect of task position on performance.

2.8.3 Measures

The Arizona Cognitive Test Battery (ACTB) (Edgin et al, 2010a) is a battery of cognitive tasks, designed to assess cognitive function in people with Down's syndrome. It includes tasks from the CANTAB as well as a few additional tasks. It has been developed by the Down Syndrome Research Group, Department of Psychology, University of Arizona.

The ACTB has been validated for use in children and adults with Down's syndrome, until the age of 35. It assesses cognitive functioning in three domains: prefrontal, hippocampal and cerebellar areas. Tests that assess prefrontal functioning are the Modified dots task (which assesses inhibitory control and working memory) and CANTAB Intra-Extra Dimensional Set Shift (set shifting). Hippocampal function is assessed by the CANTAB Paired Associates Learning task (spatial associative memory) and Virtual computer generated Arena (spatial memory). Cerebellar functions are assessed using the Finger sequencing task (motor sequencing), NEPSY visuomotor precision (visuo-motor tracking and hand-eye coordination) and the CANTAB Simple Reaction Time (motor response time and attention).

The ACTB is becoming increasingly recognised as a suitable cognitive assessment battery for people with Down's syndrome (Patterson et al, 2013; Dierssen, 2012) and is starting to be used in the UK as well as in the USA.

The CANTAB eclipse (Cambridge Neuropsychological Test Automated Battery) is a set of computerised cognitive assessment tests designed to assess cognitive functions in different domains. It has been developed by Cambridge Cognition, who are based in Cambridge, England. Some of the CANTAB tests have been used in studies with older adults without dementia (Robbins et al, 1994) and in studies with older adults with dementia or mild cognitive impairment (Egerhazi et al, 2007; Facal et al, 2009).CANTAB tasks have also been used in studies examining other conditions, including Schizophrenia, Mania, Depression and Parkinson's disease.

The tests require the use of a touchscreen computer tablet. The computer tablet that was used in this study was the Paceblade Slimbook 200, which used a Windows XP operating system and has a screen size of 12.1 inches.

In this thesis, I will refer to the ACTB tests and the table top tests as cognitive tests. I will refer to the informant rated assessments as carer rated assessments. A number of tasks used in this study, including those from the ACTB, table top and carer rated assessments, generate a number of different scores and sub-scores that can be used for analysis. Both the CANTAB guidance and the original ACTB paper (Edgin et al, 2010a) refer to these as outcome measures, and for consistency, I will also refer to them as outcome measures in this thesis.

It should be noted that although NEPSY visuomotor precision is undertaken using a pencil and paper, it is part of the Arizona Cognitive Test Battery (ACTB), and I have therefore included it within sections on the ACTB.

2.8.4 Primary outcome

2.8.4.1 CANTAB Paired Associates Learning (PAL)

The primary outcome for this study was the CANTAB PAL score. The CANTAB PAL measures paired associates learning, which taps into spatial associative memory. It has been shown to distinguish between those with Alzheimer's disease and those without Alzheimer's disease in the general population (Swainson et al, 2001) and is being marketed by Cambridge Cognition as a tool that General Practitioners can use to detect Alzheimer's disease. It has been used in research with children and adults with Down's syndrome (Oliver et al, 1998; Visu-Petra et al, 2007; Edgin et al, 2010; Edgin et al, 2011) and in clinical trials (Boada et al, 2012).

In this task, participants are shown six white squares, which represent boxes, on a touchscreen computer tablet. These open up in turn, revealing patterns behind some of the boxes. This is demonstrated in Figure 2.1. Participants

then need to identify which pattern was in which box. The stages range from 1 pattern in 1 of 6 boxes, to 8 boxes each with 8 different patterns. There are 8 stages in total. Participants have ten trials at each stage before the programme will terminate.

Figure 2.1 – CANTAB PAL
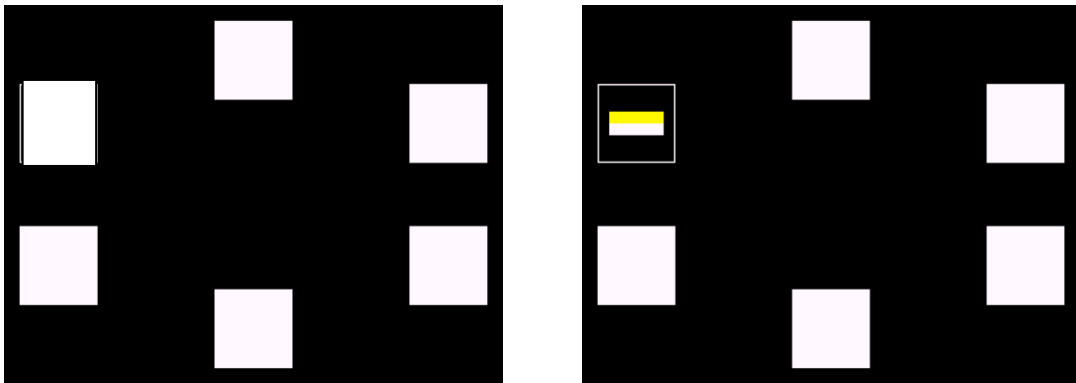
There is a version of the CANTAB PAL for people with Down's syndrome in development, however this was not available at the time that this study was conducted. In this study, I used the clinical mode, which is the recommended mode to use and was used in the original ACTB study.

There are several outcome measures generated from this task. I have reported two outcome measures in this study: first trial memory score and stages completed. First trial memory score gives the number of patterns correctly identified at the participant's first trial or attempt. This is the outcome measure reported in the ACTB study and is the outcome measure I based my power calculation on. However, in this study, a more appropriate outcome measure to use was stages completed, which refers to the number of stages which were completed by the participant and has a better spread of data in my study sample. I have therefore reported both of these outcome measures in this thesis.

2.8.5 Secondary outcomes

2.8.5.1 ACTB tests

2.8.5.1.1 CANTAB Intra-Extra Dimensional Shift (IED)

This is a measure of prefrontal function and measures set shifting. In this task, participants are shown a computer screen with two purple patterns. Participants are asked to work out the rule and press the box with the pattern in it that they have identified as "right". Once participants have identified the rule, the rule then changes and participants have to work out the new rule. The test becomes increasingly complex and more advanced stages include white lines as well the purple patterns. Figure 2.2 shows the CANTAB IED.

Participants need to have 6 consecutive correct responses before moving to the next stage. If they are unable to reach this after 50 trials, the task ends. Different stages are reported to assess different cognitive functions. The first stage measures simple discrimination learning and the second stage measures reversal learning. The intra dimensional shift occurs at stage 6, when new patterns and lines are displayed. The rule is still based on identifying what the "right" pattern is. The extra dimensional shift occurs when participants have to identify that the new rule depends on the white line rather than the pattern. This occurs at stage 8. There are 9 stages in total.

There are several outcome measure in this task. The outcome measures used in this study are stages completed and errors block 1. Errors block 1 refers to the number of errors made in the first stage, which measures simple discrimination learning. I used the clinical mode for this task.

Figure 2.2 - CANTAB IED
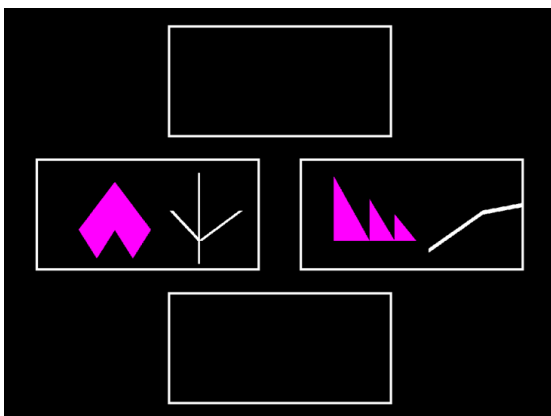
As well as being used in the ACTB, this task has been used in research with young adults with Down's syndrome and young adults with Fragile X syndrome in the Netherlands (van der Molen et al, 2012).

2.8.5.1.2 Modified dots task (Cats and Frogs)

This is a computer based task developed by the Department of Psychology, University of Arizona. It is a test of inhibitory control and working memory. In the first stage of the task, participants are taught a rule for which button to press when a picture of a cat comes on the screen (press the button directly below the cat). They are then taught a new rule for when a frog comes on the screen (press the button on the opposite side of the screen from the frog). In the third and final stage of this task, participants are then required to shift between the cat and frog rules when either cats or frogs are shown on the screen.

This task requires the computer software Presentation (www.neurobs.com), in order to run. The outcome measures used in this study are percentage of correct presses in the 2nd stage, when participants need to learn the reverse of the previous rule and percentage of correct presses in the 3rd stage, when participants need to switch between the cat and frog rules.

This task has been used in children and young adults with Down's syndrome in the USA (Edgin et al, 2010a).

2.8.5.1.3 CANTAB Simple Reaction Time (SRT)

This task was designed by CANTAB to be a measure of attention, but was incorporated into the ACTB as a measure of cerebellar function and assesses motor response time. Participants are shown a black computer screen. At times, a white square appears in the centre of the screen. This is demonstrated in Figure 2.3. Participants are asked to press a button on a press pad as soon as they see the white square. There is a variable time in between when the white square appears on the screen.

There are three sections in this task, which do not change in degree of difficulty. The score for analysis that was used in this study was the median latency score. Other scores that are available to use include number of correct trials (out of a total of 124 trials), which can give a measure of attention.

Figure 2.3 – CANTAB SRT

2.8.5.1.4 Finger sequencing task (Fingertapping)

This is a computer based task that assesses motor sequencing. It is based on the NEPSY fingertapping task, but was adapted by the Department of Psychology, University of Arizona to a computer-based version as there was a poor level of compliance with the table-top task. In the computer version, participants are asked to help the dog "run" to his food by tapping the lever.

It measures finger sequencing generated by tapping a number of fingers (from 1 to 4) on both hands to a lever in succession. The Finger sequencing task has the potential to generate a number of outcome measures, but this requires at least two researchers for scoring. I therefore obtained one simple outcome measure for this task. The score I used for analysis was maximum sequences reached.

In this study, I used a computer mouse for the first 7 participants. As participants were not familiar with using a computer mouse, they found this difficult. This was therefore changed to a lever made by the Department of Psychology, University of Arizona. For completeness, I have included data using both the mouse and the lever in this analysis.

2.8.5.1.5 NEPSY visuomotor precision

This is a table-top test that was included in the ACTB to assess visuo-motor tracking and hand-eye coordination. It is part of the NEPSY II (developmental NEuroPSYchological assessment) (Korkman et al, 2007), which is another battery of tests of cognitive abilities designed for children.

In this task, participants are asked to draw a line around a track, without going outside the track lines and without turning the paper. There are three tracks to complete. The width, length and complexity of the track increase with each track. Participants are assessed on number of errors and time taken. A score is then calculated using NEPSY tables, which takes into account errors and time taken. In this study, I used two outcome measures: one that is calculated using the first and second tracks – train and car (designed for typically developing children aged 3 to 4 and used in the original ACTB paper analyses) and one that is calculated using the second and third tracks – car and motorbike (designed for typically developing children aged 5 to 12).

2.8.5.2 Table top tests

2.8.5.2.1 Verbal fluency

This assesses initiation and set shifting and was selected from the CAMCOG-DS assessment battery (Ball et al, 2006b). In this task, participants are asked to name as many animals they can think of in one minute. Repetitions were recorded but did not contribute to the total score. The total number of animals is then adjusted using a scale, where 1-5 animals = 1, 6-10 animals = 2, 11-15 animals = 3 and 16 and over = 4. The outcome measures I have used in this thesis are the raw score and adjusted score.

2.8.5.2.2 Tower of London

This is a test of executive function and specifically assesses working memory and planning (Shallice, 1982). The test used was adapted for use with people with intellectual disability from Strydom et al (2007). In this task, the researcher and participant both have a board with a green, a red and a blue ball in a specific starting position. In the teaching phase, participants are shown a 1 move configuration on the researcher's board and are asked to move the balls in order to make their board look like the one the researcher has.

In the test phase, participants have to work out how to make other configurations with as few moves as possible. They are not allowed to move more than one ball at any one time. In this study, there were two 2- and 3-move configurations and one 4-move configuration. The Tower of London test is demonstrated in Figure 2.4. In Figure 2.4, moving the balls from the position in the left hand picture to the position in the picture on the right takes a minimum of four moves.

Figure 2.4 – Tower of London
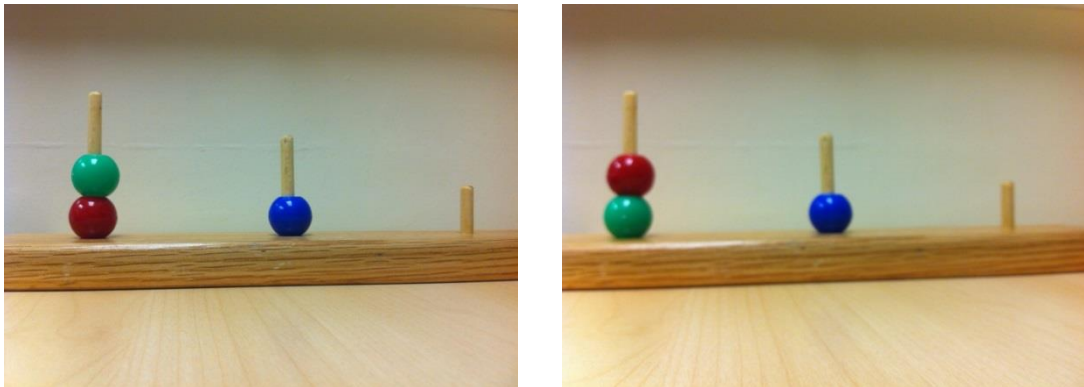
This task was scored by awarding 1 point for each configuration correct in more than the minimum moves and 2 points if it was completed in the minimum number of moves. The maximum score available was 10. I used two outcome measures in this study: points and stages completed.

2.8.5.2.3 NAID Object memory

This is a test of object memory. It forms part of the Neuropsychological Assessment of age related cognitive deficits in Adults with Down's syndrome (NAID), which is a battery of cognitive tests for people with intellectual disability often used in clinical practice and research (Crayton et al, 1998).

In the Object memory task, participants are shown ten everyday items (these are: a comb, a key, a letter, a 10p coin, a spoon, a watch, a notepad, a purse, a pencil and a toothbrush). They are asked to name them. Any items participants are not able to name are not used in testing.

In the teaching stage, participants are shown 2 items and are again asked to name them. One item is then covered and participants need to name the item that is covered. This is repeated using 3 items.

In the testing stage, two items are displayed and participants are asked to name them. Whilst the participant is looking away, one item is covered. Participants are asked to name which item is covered. This is repeated with another two items. This is then repeated with 3, 4, 5 and 6 items. There are a

total of 10 trials (i.e. 2 trials for each number of items). Between each trial, I changed a selection of items.

The outcome measure for this task is number of items remembered. The maximum score is 10.

Figure 2.5 – NAID Object memory

2.8.5.2.4 NAID Memory for sentences

This assesses verbal memory and is also part of the NAID. During the teaching phase, the assessor asks the participant to repeat the words "watch" and "lamp" back to them. During the testing phase, participants are asked to repeat back a sentence. The sentences get progressively longer. Participants are scored on how many words in the sentence they are able to repeat. The maximum score for this task is 48.

Object memory, Memory for sentences, Verbal fluency and the Tower of London test have previously been used in a study with older people with Down's syndrome (Ball et al, 2008). The standardised NAID manual is yet to be published.

2.8.5.2.5 Standardised Finger-nose test

This is a clinical test used to assess cerebellar function. Participants are asked to touch their nose and then touch a red spot of 2cm diameter which is 45 cm away from them. The outcome measure is the number of times they can do this in 20 seconds.

This standardised version has been used to assess motor coordination in older adults in the general population (Desrosiers et al, 1995).

2.8.5.2.6 Gait assessment

To assess gait, I used the timed up and go test. This is a clinical assessment that can be used to assess balance, and includes rising, walking and turning. Participants are timed to see how long it takes for them to get up from a chair, walk a distance of 3 meters, turn around, walk back to the chair and sit back down (Podsiadlo and Richardson, 1991). Participants have one practice and then two testing trials. An average of the two testing trials is the outcome measure. Where participants were only able to complete the practice trial, this was included in the analysis for completeness.

2.8.5.3 Carer rated assessments

2.8.5.3.1 Dementia Questionnaire for people with Learning Disabilities (DLD)

This is a carer rated questionnaire which is often used clinically to assist in the identification of dementia in people with intellectual disabilities (Evenhuis, 1992; Evenhuis, 1996). Carers are asked to rate various items relating to the cognitive and social function of the individual with intellectual disability over the past two months. Sums of cognitive scores (SCS) and sums of social scores (SSS) are calculated, which combine to form a total score. A deterioration in score can help clinicians when making a diagnosis of dementia. A higher score is indicative of increased difficulties. Sub-sections of the Cognitive Scores are Short Term Memory (STM), Long Term Memory

and Spatial and Temporal Orientation. Sub-sections of the Social Scores are Speech, Practical skills, Mood, Activity and Interest and Behavioural disturbance. The maximum scores for sum of cognitive and social scores are 44 and 60 respectively, making a maximum total score of 104.

The DLD was previously known as the DMR (Dementia Questionnaire for persons with Mental Retardation). The DLD has been used extensively both clinically and in research with people with intellectual disabilities, including those with Down's syndrome (Strydom and Hassiotis, 2003; Strydom et al, 2007; Lott et al, 2012).

2.8.5.3.2 Behaviour rating inventory for executive function (BRIEF)

The BRIEF - Parent Form (Behaviour Rating Inventory of Executive Function) is a carer rated assessment of executive function (Gioia et al, 2000). It is an 86 item questionnaire for use for people between 5-18 years. It takes approximately 10 -15 minutes to administer and 20 minutes to score. Carers rate behaviours in the past 6 months according to whether the behaviour has occurred Never, Sometimes or Often. Results are then calculated to generate 8 subscale scores. These are: Inhibit, Shift and Emotional control (which make up the Behavioural Regulation Index (BRI)), and Initiate, Working memory, Plan/organise, Organisation of materials and Monitor (which make up the Metacognition Index (MI)). Together, the Behavioural Regulation Index and the Metacognition Index make up the Global Executive Composite (GEC). There are parent rated, teacher rated, pre-school and adult versions of the BRIEF. In this study, I adapted the parent version for use in an adult population. This measure has not been validated in an adult population, but has been used in the original ACTB study (Edgin et al, 2010a).

Results are not valid if more than 14 questions are not answered and questionnaires that had more than 14 questions not answered were not used in the analysis. Some questions are also used to generate Negativity and Inconsistency scales, which can be used to help the researcher when considering validity. The negativity scale is scored as acceptable, elevated or

highly elevated. A highly elevated negativity scale implies that raters have reported a number of questions negatively. The inconsistency scale is scored as acceptable, questionable or inconsistent. Where participants had a highly elevated negativity score and an inconsistency score of questionable/inconsistent, or an elevated/highly elevated negativity score and an inconsistency score of inconsistent, the BRIEF scores were removed from the analysis.

Raw scores should then be converted to population-based percentiles. As the published percentiles are based on children and this study was conducted with adults, I used the raw scores in my analysis.

2.8.5.3.3 PAS-ADD checklist

The PAS-ADD checklist is a clinical screening tool that has also been used in research to screen for mental health problems (Moss et al, 1998). Carers are asked to rate symptoms over the past 4 weeks. Scores are rated as to whether a participant has passed the threshold score for each specific category.

Although designed for clinical practice, the PAS-ADD checklist has been used in a number of studies with people with intellectual disabilities (Cooper et al, 2009b), including those with Down's syndrome (Mantry et al, 2008).

2.8.6 Summary of cognitive assessments

Table 2.1 shows a summary of the cognitive assessments used in this study.

Table 2.1 – Summary of cognitive assessments

	ACTB	Table top tests	Carer rated assessments
Prefrontal	CANTAB IED (Intra-Extra Dimensional Shift)	Verbal fluency (CAMCOG-DS)	BRIEF
	Modified dots task (Cats and Frogs)	Tower of London	
Hippocampal	CANTAB PAL (Paired Associates Learning)	Object memory (NAID)	DLD
		Memory for sentences (NAID)	
Cerebellar	CANTAB SRT (Simple Reaction Time)	Standardised Finger-nose test	
	Finger sequencing task (Fingertapping)	Gait assessment	
	NEPSY visuomotor precision		

2.8.7 Other tests

2.8.7.1 K-BIT II

The K BIT II (Kaufman Brief Intelligence Test) is a measure of verbal and non-verbal intelligence and is appropriate for use for people between 4 and 90 years of age (Kaufman and Kaufman, 2004).

It is a global cognitive measure that has been used by the Down's syndrome research group in the University of Arizona and is being used in similar studies. It mainly relies on non-verbal responses, so somewhat accounts for the weaker verbal skills often seen in people with Down's syndrome. It has been used widely in US populations and the K-BIT has recently been used in a UK sample of people with intellectual disability (Tyrer et al, 2010).

The K-BIT II generates separate verbal and non verbal raw subscales, which are combined to give a total raw score. These should then be converted to population norms, however, a large proportion of participants in my sample would have scored at floor, as the K-BIT II is not able to determine the level of IQ below 40. I therefore used the raw scores in my analysis. The original ACTB paper also uses raw K-BIT scores.

2.8.7.2 CANTAB MOT (Motor Screening Task)

This is a CANTAB teaching test, designed to assess whether participants are able to use the touchscreen computer tablet. Participants are shown flashing crosses on a screen and the researcher demonstrates how to make them disappear by touching them. Then participants are asked to try to make the crosses disappear by touching them. Participants were given several attempts to do this task. If they were not able to touch the cross on at least one occasion, they were seen as not passing the teaching stage for the computer tasks and did not attempt the rest of the computer-based tasks. In this study, I used the high visibility mode. Figure 2.6 shows the CANTAB MOT computer screen.

Figure 2.6 – CANTAB MOT

2.8.7.3 Physical health tests

In order to obtain basic measures of health, I obtained blood pressure and pulse readings as well as abdominal circumference. If participants or their carers had recent weight and height measurements, I obtained these as well. Weight and height were converted into metric units if applicable.

2.8.7.4 Data Collection

Demographic and other important information was collected on a data collection form. This included:

- Demographic details - Age, Gender, Ethnic origin, type of accommodation, family history of Down's syndrome, family history of dementia
- Level of intellectual disability and premorbid cognitive level (IQ), if known
- Medical problems (including hypothyroidism, epilepsy, history of CVA, falls)
- Psychiatric history
- Sensory impairments
- Medication

2.8.7.4.1 Dementia diagnosis

Dementia diagnosis was obtained by asking at the time of assessment if the participant had a diagnosis of dementia. Where applicable, the status of a dementia diagnosis at the time of assessment, (or subsequently made by the treating clinician directly based on the findings of the assessment) was clarified from the clinical notes and/or by discussing this with the participant's treating clinician. A consensus dementia diagnosis was then decided on by myself in consultation with my primary supervisor (ASt), taking into account the treating clinician's dementia diagnosis and other relevant factors such as new onset of epilepsy.

Participants were categorised into either a "dementia" or "no dementia group". Those in the dementia group had a diagnosis of dementia or possible dementia. Those in the no dementia group had no diagnosis of dementia. Some participants in the no dementia group had symptoms of cognitive concern, which may have been explained by other factors or were not enough to warrant a diagnosis of dementia.

2.9   Analysis

Data were entered into a database using SPSS version 21. The majority of the analyses were conducted using SPSS. Stata IC12 was used to calculate the median difference and 95% confidence intervals for the non-parametric analyses.

2.9.1   Demographics

I initially described the demographic profiles of the total sample and then looked for any differences between those with dementia and those without dementia.

2.9.2 Feasibility

Feasibility tests were used to assess the psychometric properties of the computer and table top tests. These included looking at the percentage of participants who were able to attempt the tests and the spread of the results. I examined these properties initially by looking at the total sample and then I looked separately at the dementia and no dementia groups.

I calculated the percentage of participants at floor and ceiling for each of the tasks. For the majority of the tasks, floor was calculated as a score of zero (for: K-BIT II total raw score, K-BIT II verbal and non verbal subscales, CANTAB PAL stages completed and first trial memory score, CANTAB IED stages completed, Finger sequencing task, NEPSY visuomotor precision, Verbal fluency raw score and adjusted and Finger-nose test). For NAID Object memory, NAID Memory for sentences, Tower of London points and stages completed, floor was calculated as a score of zero and/or did not pass teaching stage. For Gait assessment, floor was calculated as being unable to mobilise without assistance.

In the modified dots task, floor was calculated as 50% or under (as 50% of responses should be correct by chance alone). CANTAB SRT median latency is measured in units of time and, as it is on a continuum, floor and ceiling levels are not applicable.

Where applicable, ceiling levels were calculated as maximum possible score.

Many of the computer based tests and some of the table top tests generated several different outcome measures. In order to identify the most valid outcome measures and ones that retained the most amount of information, I initially narrowed them down to the ones that had good face validity, for example, some of the CANTAB outcome measures provide adjusted scores that would not be valid if the majority of participants did not complete all levels of the task. I also discussed which would be the most appropriate measures to use with one of the authors of the ACTB.

Following data collection, I looked at the range and spread of the data for the relevant outcome measures as well as the proportion of those at floor and whether those at floor were able to be used in data analysis or not. In consultation with my primary supervisor (ASt), we came to a consensus about which outcome measure for each test would be the most appropriate to use. Alongside this, I also considered which outcome measures were commonly used in the relevant literature in this population.

Where it was not clear what the most appropriate outcome measure was to use for a specific test, I have reported data on more than one outcome measure.

The spread of the data and distribution was assessed using box and whisker plots. The majority of data was not found to be normally distributed and therefore non-parametric statistical tests are used for the majority of analyses.

2.9.3 Differences between dementia and no dementia groups

2.9.3.1 Primary analysis

My primary outcome was the difference in the CANTAB PAL first trial memory score between the dementia and no dementia groups. I also analysed CANTAB PAL stages completed.

2.9.3.2 Secondary analyses

Following my primary analysis, I examined the differences between the dementia and no dementia groups in the other cognitive tests, including the scores of the other tests in the ACTB. As the data was not normally distributed, on the recommendation of the statistician assisting in this study (KR), this was assessed by examining the median difference and 95% confidence intervals between the two groups.

2.9.3.3 Analyses adjusting for confounders

For the cognitive tests where the 95% confidence intervals for the median difference between the dementia and no dementia groups did not include zero, I then used appropriate statistical models to identify whether a statistically significant difference remained when accounting for age and gender.

2.9.4 Concurrent validity

I assessed the relationship between the tests in the ACTB and other measures of cognitive function (table top tests and carer ratings) using correlation. I calculated the Spearman's rank correlation coefficient between the ACTB, table top and carer rated tests that assessed prefrontal, hippocampal and cerebellar function.

2.10 Summary

Adults with Down's syndrome aged 45 and over were recruited. Specific cognitive skills of participants with Down's syndrome were assessed using a number of cognitive tests. The assessment lasted between 2-3 hours and was arranged at a location that was convenient for the participant and their carer.

The assessment included computer-based tests (the Arizona Cognitive Test Battery, ACTB) and table-top tests, which were designed to assess cognitive function in the prefrontal, hippocampal and cerebellar areas. Alongside this, carers or relatives completed carer-rated questionnaires.

Chapter 3. Results
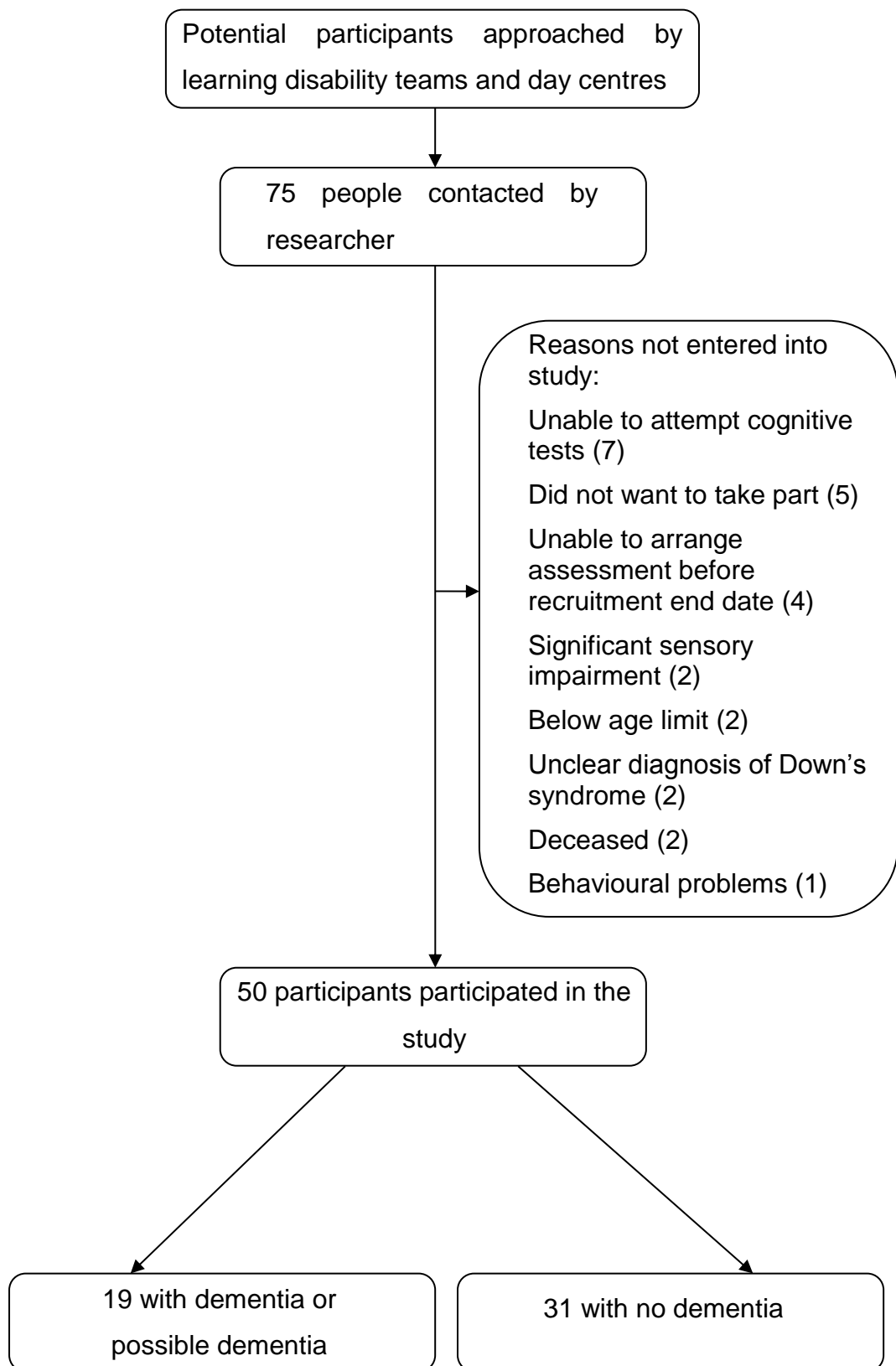
Chapter 3. Results

3.1 Overview

The main aim of this study was to assess the use of the ACTB in older adults with Down's syndrome and establish its validity in testing for dementia. I will begin this chapter by describing the demographic characteristics of the sample. I will then present results regarding feasibility of the tasks as well as examining differences between the dementia and no dementia groups. I will conclude by describing the concurrent validity of the tasks.

3.2 Flow diagram

Figure 3.1 summarises the flow of participants in the study. As the first stage of recruitment was conducted by local learning disability teams and day centres, there is no record of how many people were initially considered for participation in the study.

Please note, when reporting and discussing my results, I will refer to the two groups as "dementia" and "no dementia" groups, however participants in the "dementia" group had a diagnosis of dementia or possible dementia and participants the "no dementia" group included some participants with symptoms of cognitive concern, which may have been explained by other factors or were not enough to warrant a diagnosis of dementia.

Figure 3.1 - Flow Diagram

Potential participants approached by learning disability teams and day centres

↓

75 people contacted by researcher

→ Reasons not entered into study:

Unable to attempt cognitive tests (7)

Did not want to take part (5)

Unable to arrange assessment before recruitment end date (4)

Significant sensory impairment (2)

Below age limit (2)

Unclear diagnosis of Down's syndrome (2)

Deceased (2)

Behavioural problems (1)

↓

50 participants participated in the study

19 with dementia or possible dementia   31 with no dementia

3.3 Demographics

50 participants were recruited into the study. Of these, 23 (46%) were male and 27 (54%) were female. Participants were recruited from the London Boroughs of Islington, Camden, Haringey, Westminster, Brent, Enfield, Hillingdon, Harrow and Kensington and Chelsea. The mean age at first assessment was 53.01 years (SD: 6.34) and the median age was 50.85 years (range: 45.14 – 67.13 years).

Average age at first assessment for the dementia group was mean 55.64 years (SD 6.77), median 55.04 years (range: 45.37 - 64.88 years). Age at first assessment for the no dementia group was mean 51.40 years (SD: 5.58), median 50.20 years (range 45.14 - 67.13 years).

There was a significant difference in age of participants between the dementia and non dementia groups, with participants in the dementia group being older. There was no significant difference in gender, level of intellectual disability, ethnic origin or type of accommodation between the two groups.

Three participants had a diagnosis of mosaic Down's syndrome documented in the clinical notes. Of these participants, one had a diagnosis of dementia.

Table 3.1 shows further detail on demographic characteristics of the group. Demographic data for the whole group as well as data for the dementia and no dementia groups are shown separately. The numbers in brackets are percentages within each group. The p-value refers to the Chi-squared or Fisher's exact test used to identify any significant differences between the dementia and no dementia groups.

The Fisher's exact p value for age as a categorical variable is shown in Table 3.1. When age was analysed as a continuous variable using the Independent samples Mann Whitney U test, the significance level was also p=0.049.

Table 3.1 - Demographic characteristics of the study sample

		Whole group/n (%)	Dementia/n (%)	No Dementia/n (%)	P value
Gender	Male	23/50 (46.0%)	12/19 (63.2%)	11/31 (35.5%)	
	Female	27/50 (54.0%)	7/19 (36.8%)	20/31 (64.5%)	0.057[a]
Age	Below 50	20/50 (40.0%)	6/19 (31.6%)	14/31 (45.2%)	
	50 – 54	14/50 (28.0%)	3/19 (15.8%)	11/31 (35.5%)	
	55 – 59	5/50 (10.0%)	2/19 (10.5%)	3/31 (9.7%)	
	60 and over	11/50 (22.0%)	8/19 (42.1%)	3/31 (9.7%)	0.049[b]*
Premorbid Level of ID					
	Mild	13/35 (37.0%)	5/14 (35.7%)	8/21 (38.1%)	
	Moderate/Severe	22/35 (63.0%)	9/14 (64.3%)	13/21 (61.9%)	0.886[a]
Ethnic origin	White	41/49 (83.7%)	17/19 (89.5%)	24/30 (80.0%)	
	African/Afrocaribbean	4/49 (8.2%)	1/19 (5.3%)	3/30 (10.0%)	
	Other	4/49 (8.2%)	1/19 (5.3%)	3/30 (10.0%)	0.738[b]
Type of Accommodation					
	Family or friends	14/50 (28.0%)	6/19 (31.6%)	8/31 (25.8%)	
	Adult placement	7/50 (14.0%)	1/19 (5.3%)	6/31 (19.4%)	
	Supported accommodation	29/50 (58.0%)	12/19 (63.2%)	17/31 (54.8%)	0.428[b]

[a] Chi Squared value, [b] Fisher's exact value, *Significant at the 0.05 level

Figure 3.2 shows the numbers of participants with and without dementia recruited from each site.

Figure 3.2 - Bar chart to show participants recruited from each site
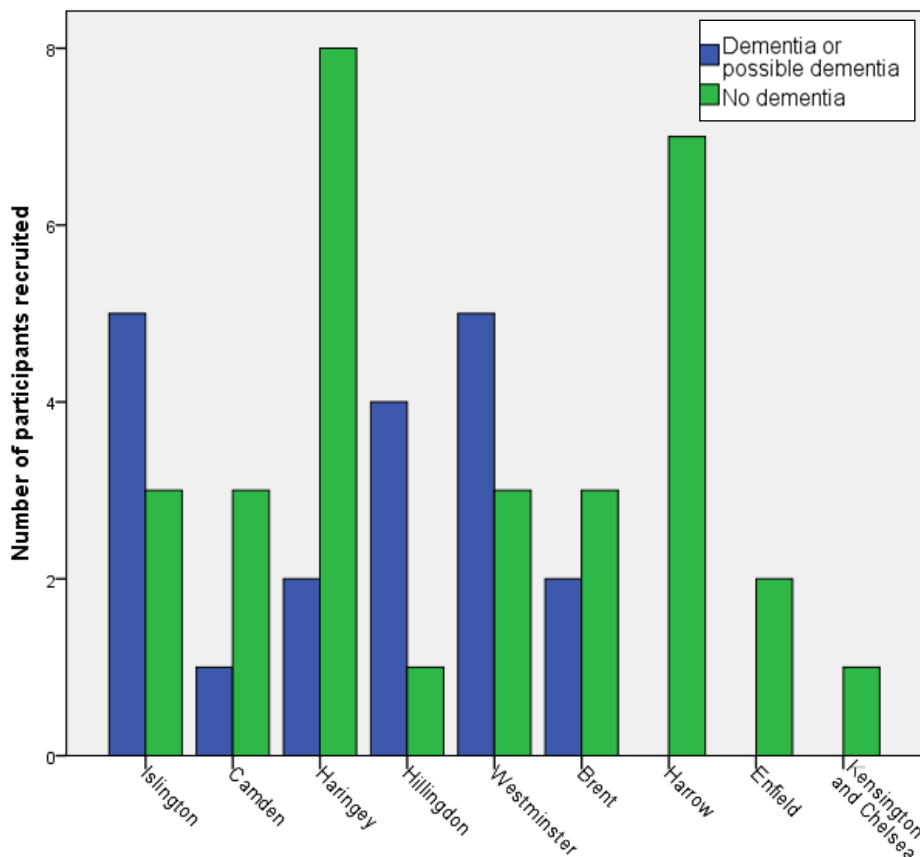
3.3.1 Physical Health

Five participants had hypercholesterolaemia and two had a history of hypertension. One participant had a diagnosis of diabetes (diet controlled Type II diabetes) and two participants were smokers. Thirteen participants had skin problems, including psoriasis and dermatitis. Five participants had abdominal problems, including abdominal pain and irritable bowel syndrome. Two participants were on anticoagulant treatment for deep vein thrombosis (DVT).

None of the participants had a confirmed history of stroke or head injury, although details of history of stroke were missing in two participants and details of history of head injury were missing in four participants. One

informant was uncertain as to whether the participant had a history of head injury.

One participant had possible congenital cardiovascular problems and one participant had possible hearing problems. These data have been taken out for the purpose of the analyses in the table below.

The frequency of physical health problems associated with Down's syndrome or dementia are described in Table 3.2. Median data for physical health measures are reported in Table 3.3.

Table 3.2 - Physical health conditions of the study sample

	Whole group/n (%)	Dementia/n (%)	No Dementia/n (%)	P value
Thyroid problems	20/49 (40.8%)	7/18 (38.9%)	13/31 (41.9%)	0.834[a]
Epilepsy	9/49 (18.4%)	5/19 (26.3%)	4/30 (13.3%)	0.282[b]
Falls	9/45 (20.0%)	4/16 (25.0%)	5/29 (17.2%)	0.700[b]
Congenital Cardiovascular problems	5/48 (10.4%)	2/18 (11.1%)	3/30 (10.0%)	1.000[b]
Hearing problems	8/47 (17.0%)	5/18 (27.8%)	3/29 (10.3%)	0.230[b]
Visual problems	23/49 (46.9%)	10/19 (52.6%)	13/30 (43.3%)	0.525[a]
Family history of dementia	7/33 (21.2%)	1/12 (8.3%)	6/21 (28.6%)	0.223[b]

[a] Chi Squared value
[b] Fisher's exact value

Table 3.3 - Physical health measures of the study sample

	Whole group Median (Range)	Dementia Median (Range)	No Dementia Median (Range)	P value [c]
Pulse (bpm) n=36	64.5 (42.0-93.5)	65.5 (52.0-82.0)	63.0 (42.0-93.5)	0.713
Diastolic BP (mmHg) n=36	71.5 (58.0-100.0)	74.8 (63.5-100.0)	70.8 (58.0-92.0)	0.160
Abdominal circumference (cm) n=40	101.3 (83.0-136.0)	97.0 (83.0-115.0)	107.0 (85.0-136.0)	0.039*
Weight (kg) n=25	72.1 (49.0-136.5)	64.9 (56.3-82.0)	82.6 (49.0-136.5)	0.344

[c] Independent samples Mann Whitney U test
* Significant at the 0.05 level

There were no significant differences in common physical health conditions between the dementia and no dementia groups. There was no significant difference in pulse, diastolic blood pressure or weight between the two groups, although there was a significant difference in abdominal circumference, with those in the no dementia group having a larger abdominal circumference.

3.3.2 Mental Health

Table 3.4 shows the frequency of mental health problems in the study sample. One participant had a history of Bipolar Affective Disorder.

Table 3.4 - Mental health conditions in the study sample

	Whole group/n (%)	Dementia/n (%)	No Dementia/n (%)	P value
History of Psychosis	7/46 (15.2%)	1/17 (5.9%)	6/29 (20.7%)	0.234[b]
History of Depression	15/46 (32.6%)	4/17 (23.5%)	11/29 (37.9%)	0.315[a]
Above PAS-ADD checklist threshold for:				
Possible organic condition	8/49 (16.3%)	4/18 (22.2%)	4/31 (12.9%)	0.443[b]
Affective or neurotic disorder	10/49 (20.4%)	6/18 (33.3%)	4/31 (12.9%)	0.141[b]
Psychotic disorder	8/49 (16.3%)	5/18 (27.8%)	3/31 (9.7%)	0.124[b]

[a] Chi Squared value
[b] Fisher's exact value

There were no significant differences in history of mental health problems between the two groups, however there was a higher percentage of participants with a history of depression and psychosis in the non-dementia group. There were no significant differences in new mental health symptoms detected in the four weeks prior to the assessment, as determined by the PAS-ADD checklist.

3.4 Feasibility

In order to evaluate feasibility of the cognitive tests, I initially examined the proportion of participants who were able to attempt each of the ACTB and table top tasks. These results are shown in Table 3.5.

Table 3.5 - Proportion of participants that attempted each cognitive task

Measure	Total attempted n=50	Dementia n=19	No dementia n=31
ACTB tests:			
CANTAB IED	45 (90.0%)	15 (78.9%)	30 (96.8%)
Modified dots task	40 (81.6%)[e]	13 (68.4%)	27 (90.0%)
CANTAB PAL	45 (90.0%)	15 (78.9%)	30 (96.8%)
CANTAB SRT	47 (94.0%)	18 (94.7%)	29 (93.5%)
Finger sequencing task	44 (89.8%)[e]	15 (79.0%)	29 (96.7%)
NEPSY visuomotor precision	41 (82.0%)	12 (63.2%)	29 (93.5%)
Table top tests:			
Verbal fluency	44 (88.0%)	14 (73.7%)	30 (96.8%)
Tower of London	37 (74.0%)	11 (57.9%)	26 (83.9%)
Object memory	34 (68.0%)	12 (63.2%)	22 (71.0%)
Memory for sentences	43 (86.0%)	14 (73.7%)	29 (93.5%)
Finger-nose	41 (82.0%)	14 (73.7%)	27 (87.1%)
Gait assessment	38 (76.0%)	12 (63.2%)	26 (83.9%)

[e] n=49

Of the ACTB tasks that were not attempted, a range from 1 (2%) to 3 (6%) of participants did not pass the teaching stage and from 1 (2%) to 4 (8%) participants refused to attempt the task. The CANTAB SRT and Finger

sequencing task were not administered on one occasion and the NEPSY visuomotor precision and Modified dots task on 2 and 3 occasions respectively. A technical issue prevented the CANTAB PAL task to be attempted on one occasion and the Modified dots task on two occasions and prevented results from being recorded from the Modified dots task on 7 occasions.

Of the table top tasks that were not attempted, a range from 2 (4%) to 6 (12%) of participants refused to attempt the task and from 1 (2%) to 8 (16%) participants did not pass the teaching stage. 4 people with dementia and 4 people without dementia did not pass the teaching stage for Object memory. Verbal fluency was not administered on one occasion, Memory for sentences and finger-nose on 2 occasions, Tower of London on 3 occasions and Object memory on 4 occasions. Gait assessment was not conducted on 5 occasions and a further 3 participants did not attempt the task, as they were not able to mobilise without assistance.

10 (52.6%) people with dementia were able to attempt all the ACTB tasks and 10 (52.6%) were able to attempt all the table top tasks. 24 (77.4%) people in the no dementia group were able to attempt all the ACTB tasks and 21 (67.7%) attempted all the table top tasks.

Table 3.6 shows the distribution data for the cognitive measures. As the outcome measures did not display a normal distribution, both the mean and median are reported.

I calculated percentage of participants at floor and ceiling for each of the tasks. See Method section 2.9.2 for further details regarding how floor and ceiling levels were determined. It is noted that some of the n for outcomes are larger than n reported in Table 3.5. This is because some outcome measures may include data from teaching phases of the tasks. Other outcome measures may have a lower n than reported in Table 3.5. This is because they may require completion up to a certain stage of the task and therefore do not include participants at floor.

Table 3.6 - Distribution data for cognitive measures

Measure	N	Mean (SD)	Median (Range)	Number at floor	Number at ceiling
K-BIT II:					
Total raw score	50	17.72 (17.77)	9.50 (1-63)	0 (0.0%)	0 (0.0%)
Verbal subscale raw score	50	12.42 (12.26)	7.5 (0-47)	1 (2.0%)	0 (0.0%)
Non verbal subscale raw score	50	5.30 (6.19)	2.0 (0-20)	10 (20.0%)	0 (0.0%)
ACTB tests:					
CANTAB IED:					
Stages completed	45	1.76 (2.68)	0 (0-8)	24 (53.3%)	0 (0.00%)
Errors block 1	45	14.67 (11.33)	15 (0-32)	n/a	6 (13.3%)
Modified dots task:					
2nd stage (frogs)	33	0.42 (0.29)	0.33 (0.0-1.0)	25 (75.8%)	4 (12.1%)
3rd stage (combined)	33	0.39 (0.17)	0.39 (0.3-0.91)	26 (78.8%)	0 (0.0%)
CANTAB PAL:					
Stages completed	45	2.56 (2.20)	2 (0-8)	6 (13.3%)	2 (4.4%)
First trial memory score	45	2.22 (3.25)	1 (0-15)	17 (37.8%)	n/a
CANTAB SRT median latency	45	1317.62 (614.37)	1300.50 (351-2408)	n/a	n/a
Finger sequencing task	43	1.72 (1.03)	1 (0-4)	1 (2.3%)	5 (11.6%)
NEPSY visuomotor precision:					
Train and car	36	10.08 (6.073)	11 (1-21)	0 (0.0%)	0 (0.0%)
Car and motorbike	34	7.62 (7.742)	4 (0-28)	1 (2.9%)	0 (0.0%)

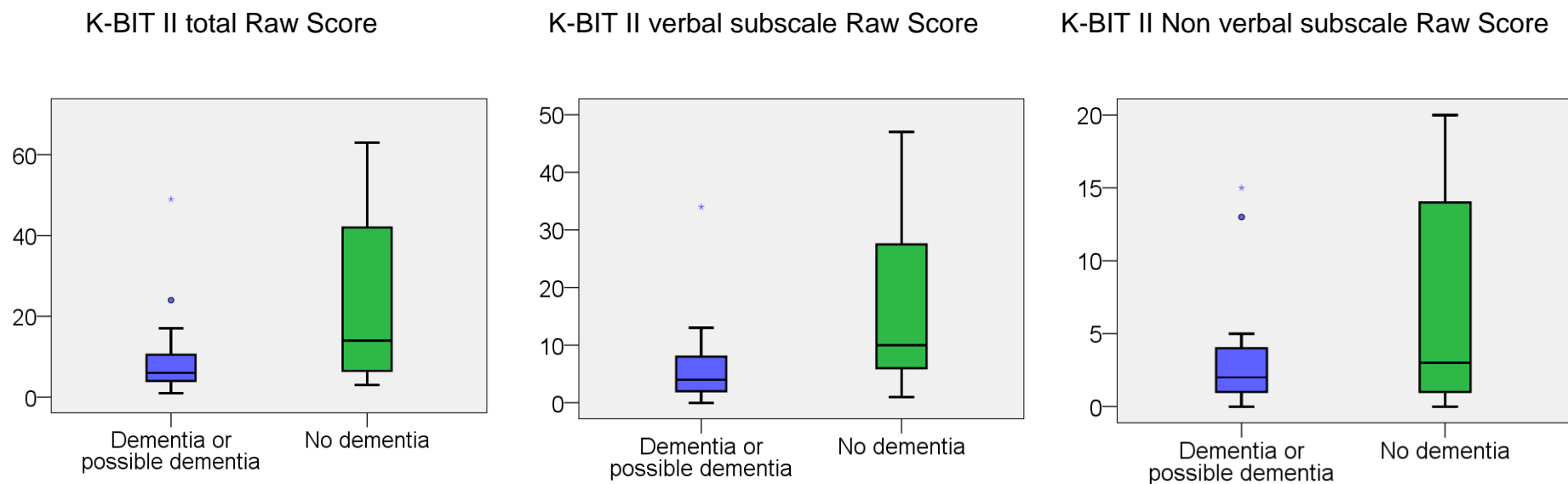| Measure	N	Mean (SD)	Median (Range)	Number at floor	Number at ceiling
Table top tests:					
Verbal fluency:					
Raw score	44	5.09 (4.03)	5 (0-17)	7 (15.9%)	n/a
Adjusted	44	1.48 (0.93)	2 (0-4)	7 (15.9%)	n/a
Tower of London:					
Stages completed	43	2.02 (1.24)	2 (0-4)	6 (14.0%)	6 (14.0%)
Points	37	3.65 (3.04)	3 (0-10)	14 (32.6%)	2 (4.7%)
Object memory	34	5.38 (2.92)	6 (0-10)	11 (26.2%)	2 (4.8%)
Memory for sentences	43	12.81 (10.76)	10 (0-44)	4 (8.5%)	0 (0.0%)
Finger-nose	41	6.32 (4.14)	6 (1-19)	0.0 (0%)	n/a
Gait assessment	38	14.61 (4.93)	14.14 (6.53-25.93)	3 (7.3%)	n/a

Table 3.6 continued – Distribution data for cognitive measures

The floor and ceiling effects vary from test to test, although the CANTAB IED stages completed and Modified dots task have a very large number of participants at floor.

Figures 3.3, 3.4 and 3.5 show boxplots comparing the outcome measures from these cognitive tasks in the dementia and no dementia groups. From these it is possible to examine the spread of the data and any differences in the medians and interquartile ranges of the dementia and no dementia groups.

As data is not symmetric around the median, it can be seen that the data does not fit a normal distribution and therefore non-parametric analyses were conducted. See Appendix Table A1 for skewness and kurtosis of these data, providing further information regarding the spread of the data.

Figure 3.3 - Boxplots to show differences between dementia and no dementia groups - K-BIT II scores

K-BIT II total Raw Score

K-BIT II verbal subscale Raw Score

K-BIT II Non verbal subscale Raw Score

Figure 3.4 - Boxplots to show differences between dementia and no dementia groups – ACTB tasks
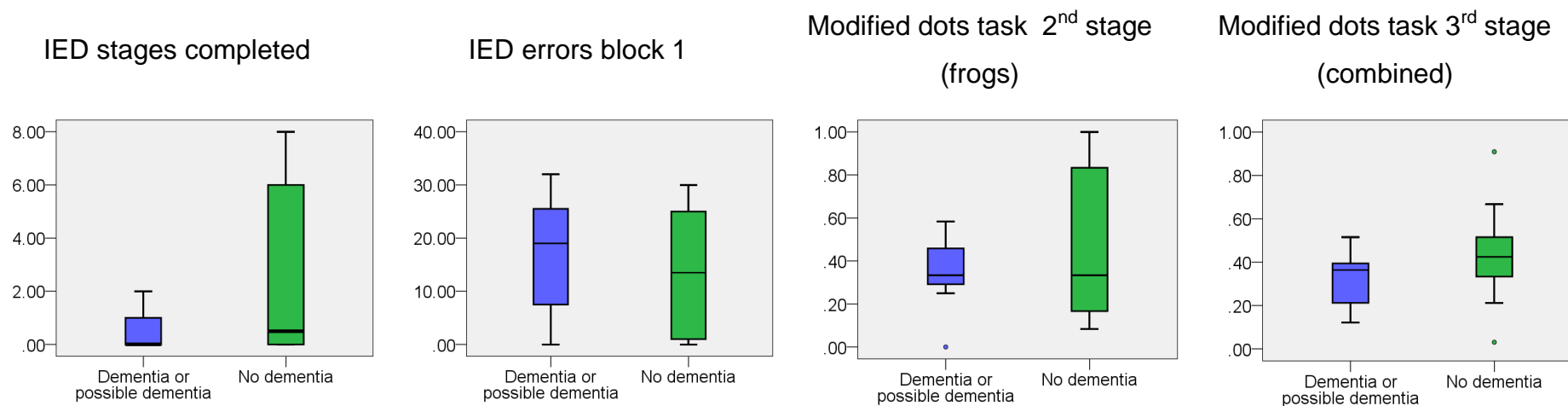
ACTB tasks - Prefrontal tasks

IED stages completed

IED errors block 1

Modified dots task 2nd stage (frogs)
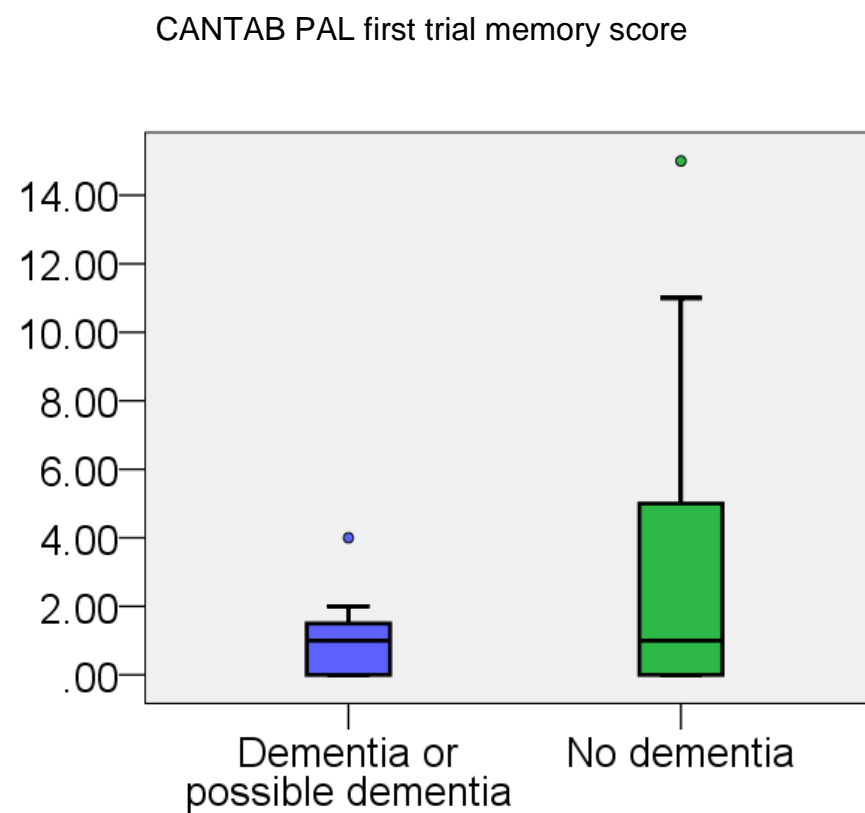
Modified dots task 3rd stage (combined)

Figure 3.4 continued - Boxplots to show differences between dementia and no dementia groups – ACTB tasks

ACTB tasks – Hippocampal tasks

CANTAB PAL stages completed
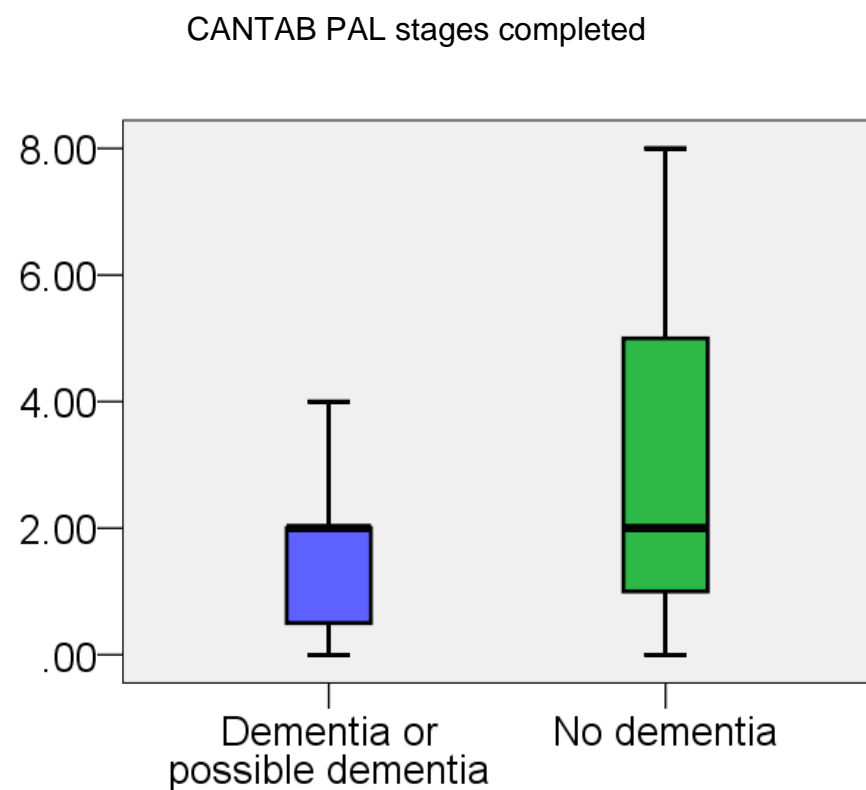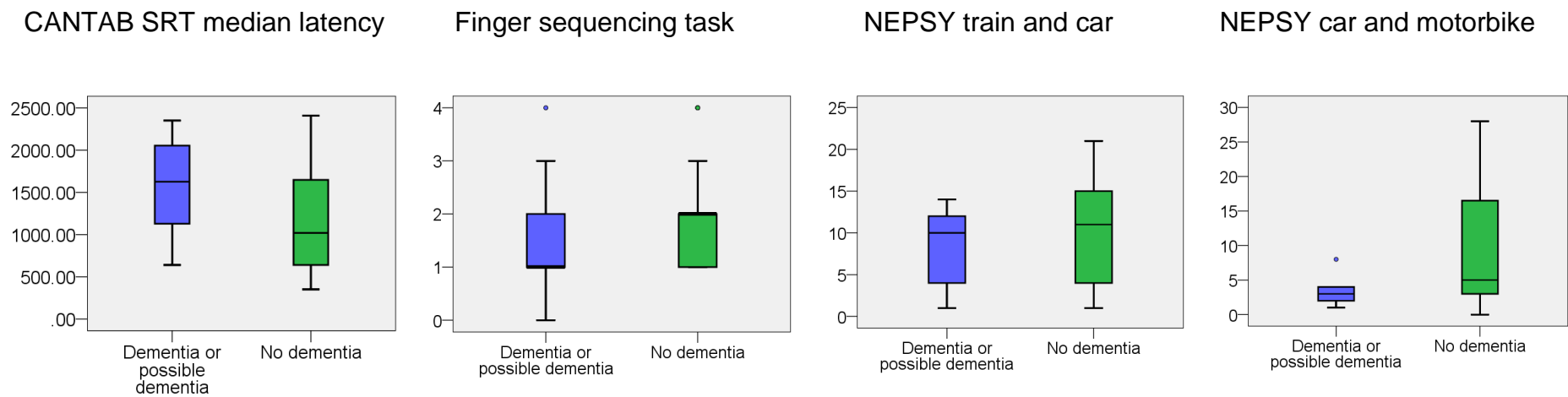
CANTAB PAL first trial memory score

Figure 3.4 continued - Boxplots to show differences between dementia and no dementia groups – ACTB tasks

ACTB tasks – Cerebellar tasks

CANTAB SRT median latency

Finger sequencing task

NEPSY train and car

NEPSY car and motorbike
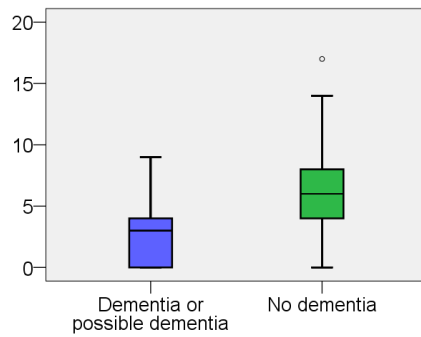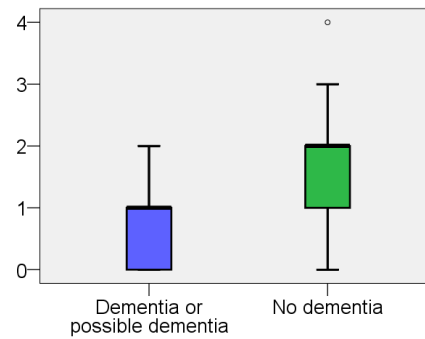
Figure 3.5 - Boxplots to show differences between dementia and no dementia groups – Table top tasks

Table top tasks – Prefrontal tasks

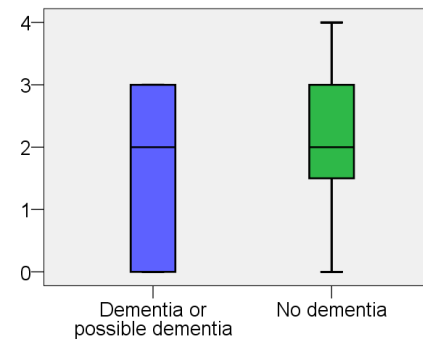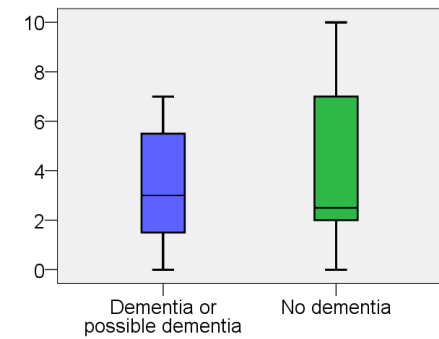| Verbal fluency raw score	Verbal fluency adjusted	Tower of London stages completed	Tower of London points

Figure 3.5 continued - Boxplots to show differences between dementia and no dementia groups – Table top tasks

Table top tasks – Hippocampal tasks

NAID Object memory

NAID Memory for sentences
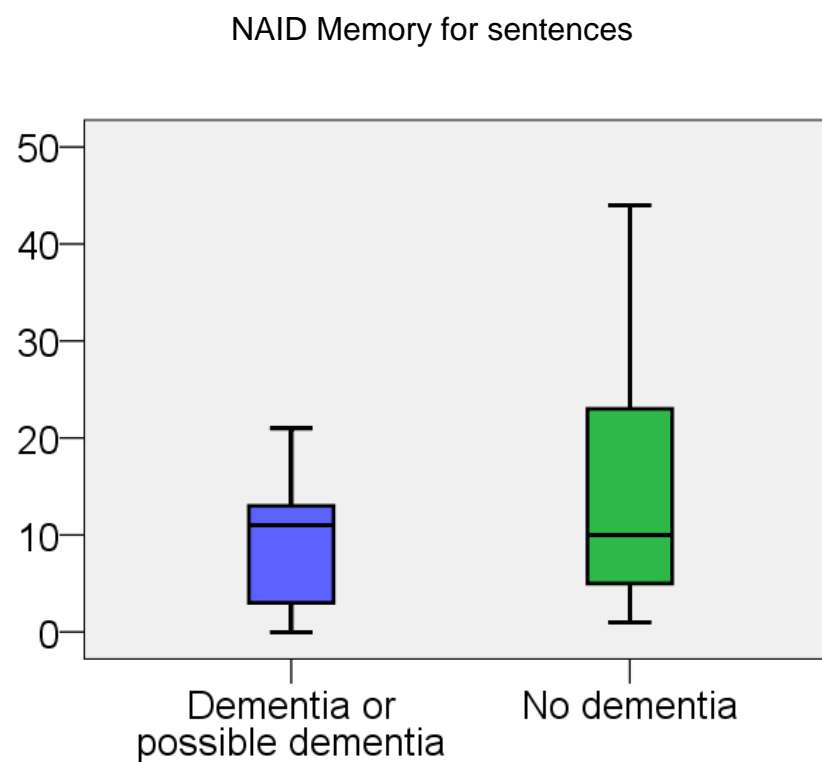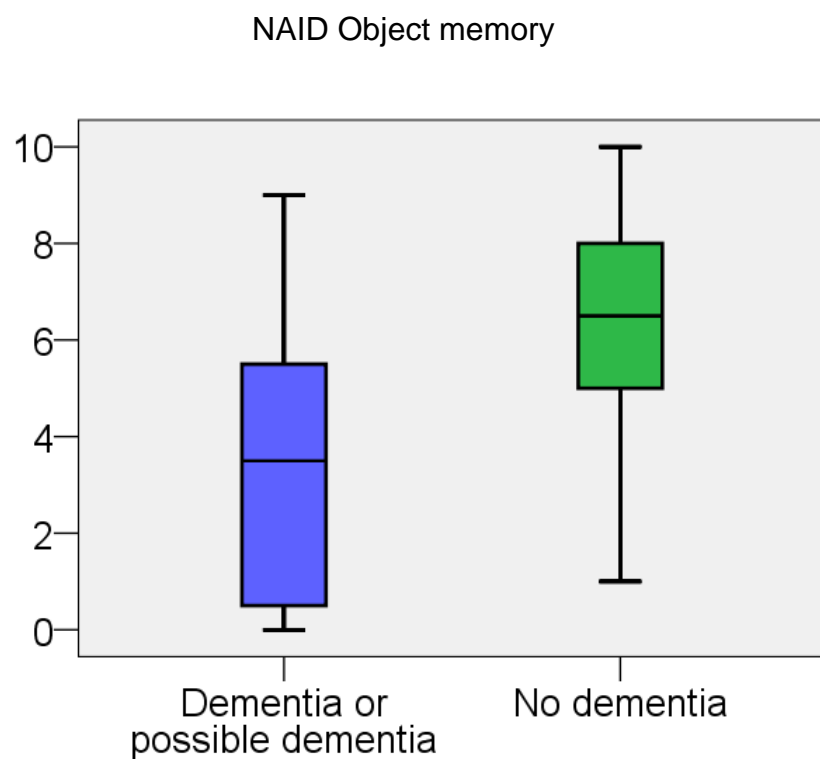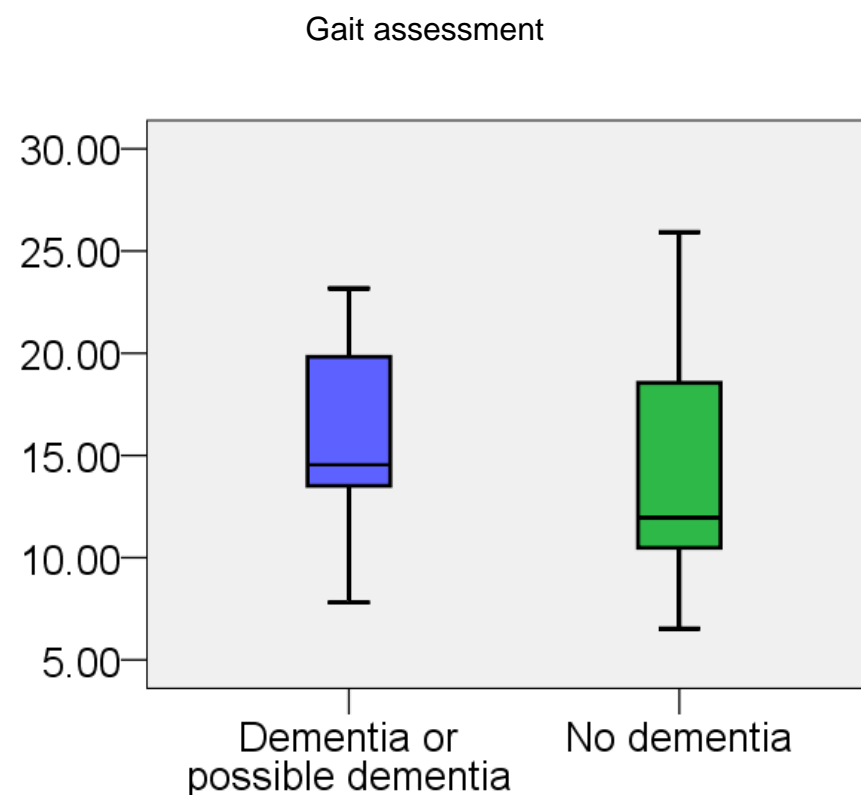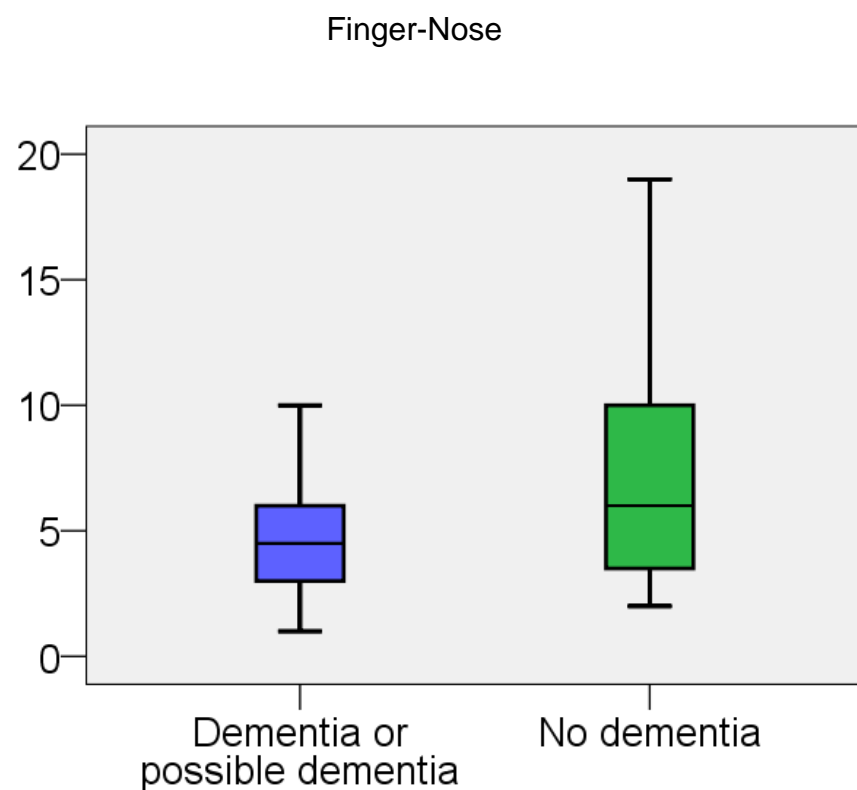
Figure 3.5 continued - Boxplots to show differences between dementia and no dementia groups – Table top tasks

Table top tasks – Cerebellar tasks

Finger-Nose

Gait assessment

3.5 Differences between dementia and no dementia groups

In my primary analyses, I assessed whether the ACTB CANTAB PAL was able to detect differences between people with Down's syndrome who have early stage dementia and those who do not.

I examined two different outcome measures from the CANTAB PAL. These were PAL first trial memory score, and PAL stages completed. The PAL first trial memory score gives the number of patterns correctly identified at the participant's first trial or attempt. This is the outcome measure reported in the ACTB study and is the outcome measure I based my power calculation on. However, I also examined PAL stages completed, which refers to the number of stages which were completed by the participant; this had a better spread of data in my study sample, due to the lower number of participants performing at floor level.

In my secondary analyses, I examined whether there were any significant differences between the two groups in any of the other ACTB cognitive tests and in the table top tests. The results, as well as further data on distribution are shown in Tables 3.7, 3.8 and 3.9.

See Appendix tables A2, 3 and 4 for further detail on floor and ceiling levels according to level of intellectual disability.

Table 3.7 - Table showing differences in cognitive tests between dementia and no dementia groups – K-BIT II scores

		Dementia					No Dementia					
	n	Mean (SD)	Median (Range)	Number at floor	Number at ceiling	N	Mean (SD)	Median (Range)	Number at floor	Number at ceiling	Median difference (95% CI)	P value [c]
K-BIT II total raw score	19	9.74 (11.06)	6 (1-49)	0 (0.0%)	0 (0.0%)	31	22.61 (19.42)	14 (3-63)	0 (0.0%)	0 (0.0%)	-6 (-20 to -2)	0.006
K-BIT II verbal subscale	19	6.53 (7.61)	4 (0-34)	1 (5.3%)	0 (0.0%)	31	16.03 (13.23)	10 (1-47)	0 (0.0%)	0 (0.0%)	-6 (-12 to -2)	0.002
K-BIT II non verbal subscale	19	3.21 (4.16)	2 (0-15)	4 (21.1%)	0 (0.0%)	31	6.58 (6.91)	3 (0-20)	6 (19.4%)	0 (0.0%)	-1 (-6 to 0)	0.253

[c] Independent samples Mann Whitney U test

Table 3.8 - Table showing differences in cognitive tests between dementia and no dementia groups – ACTB tests

	n	Mean (SD)	Median (Range)	Number at floor	Number at ceiling	n	Mean (SD)	Median (Range)	Number at floor	Number at ceiling	Median difference (95% CI)	P value [c]
		Dementia					**No Dementia**					
CANTAB PAL first trial memory score	15	0.93 (1.16)	1 (0-4)	7 (46.7%)	0 (0.0%)	30	2.87 (3.75)	1 (0-15)	10 (33.3%)	0 (0.0%)	-1 (-2 to 0)	0.131
CANTAB PAL stages completed	15	1.40 (1.12)	2 (0-4)	4 (26.7%)	0 (0.0%)	30	3.13 (2.39)	2 (0-8)	2 (6.7%)	2 (6.7%)	-1 (-2 to 0)	0.016
CANTAB IED stages completed	15	0.60 (0.83)	0 (0-2)	9 (60.0%)	0 (0.0%)	30	2.33 (3.09)	0.50 (0-8)	15 (50.0%)	0 (0.0%)	0 (-2 to 0)	0.194
IED errors block 1	15	16.5 (10.7)	19 (0-32)	n/a	2 (13.3%)	30	13.73 (11.70)	13.5 (0-30)	n/a	4 (13.3%)	3 (-3 to 9)	0.514
Modified dots task 2nd stage	11	0.36 (0.16)	0.33 (0.00 – 0.58)	10 (90.9%)	0 (0.0%)	22	0.45 (0.34)	0.33 (0.08-1.00)	15 (68.2%)	4 (18.2%)	0 (-0.333 to 0.167	0.925
Modified dots task 3rd stage	11	0.32 (0.14)	0.36 (0.12-0.52)	10 (90.9%)	0 (0.0%)	22	0.42 (0.18)	0.42 (0.03-0.91)	16 (72.7%)	0 (0.0%)	-0.09 (-0.21 to 0.03)	0.133
CANTAB SRT median latency	17	1556.5 (559.8)	1626.0 (640-2350)	n/a	n/a	28	1172.6 (609.6)	1020.0 (351-2408)	n/a	n/a	404.5 (35.5 to 763.5)	0.039
Finger sequencing task	14	1.50 (1.02)	1 (0-4)	1 (7.1%)	1 (7.1%)	29	1.83 (1.04)	2 (1-4)	0 (0.0%)	4 (13.8%)	0 (-1 to 0)	0.275
NEPSY visuomotor precision train and car	10	8.50 (4.65)	10 (1-14)	0 (0.0%)	0 (0.0%)	26	10.69 (6.52)	11 (1-21)	0 (0.0%)	0 (0.0%)	-2 (-7 to 2)	0.393
NEPSY visuomotor precision car and motorbike	10	3.20 (1.99)	3 (1-8)	0 (0.0%)	0 (0.0%)	24	9.46 (8.51)	5 (0-28)	1 (4.2%)	0 (0.0%)	-2 (-10 to 0)	0.028

[c] Independent samples Mann Whitney U test

Table 3.9 - Table showing differences in cognitive tests between dementia and no dementia groups – Table top tests

		Dementia					No Dementia				Median difference (95% CI)	P value [c]
	n	Mean (SD)	Median (Range)	Number at floor	Number at ceiling	n	Mean (SD)	Median (Range)	Number at floor	Number at ceiling		
Verbal fluency raw score	14	2.93 (2.70)	3 (0-9)	4 (28.6%)	n/a	30	6.10 (4.19)	6 (0-17)	3 (10.0%)	n/a	-3 (-5 to -1)	0.010
Verbal fluency adjusted	14	0.93 (0.73)	1 (0-2)	4 (28.6%)	n/a	30	1.73 (0.91)	2 (0-4)	3 (10.0%)	n/a	-1 (-1 to 0)	0.005
Tower of London stages completed	16	1.56 (1.26)	2 (0-3)	5 (31.3%)	0 (0.0%)	27	2.30 (1.17)	2 (0-4)	1 (3.7%)	6 (22.2%)	-1 (-2 to 0)	0.106
Tower of London points	11	3.27 (2.49)	3 (0-7)	7 (43.8%)	0 (0.0%)	26	3.81 (3.27)	2.50 (0-10)	7 (25.9%)	2 (7.4%)	0 (-2 to 2)	0.756
Object memory	12	3.50 (2.94)	3.50 (0-9)	7 (43.8%)	0 (0.0%)	22	6.41 (2.40)	6.50 (1-10)	5 (14.8%)	2 (7.4%)	-3 (-5 to -1)	0.007
Memory for sentences	14	9.71 (6.37)	11 (0-21)	3 (18.8%)	0 (0.0%)	29	14.31 (12.14)	10 (1-44)	1 (3.3%)	0 (0.0%)	-2 (-9 to 3)	0.406
Finger-nose	14	4.93 (2.92)	4.50 (1-10)	0 (0.0%)	n/a	27	7.04 (4.53)	6.0 (2-19)	0 (0.0%)	n/a	-1 (-4 to 1)	0.185
Gait assessment	12	15.76 (4.26)	14.55 (7.82-23.17)	3 (20%)	n/a	26	14.08 (5.19)	11.96 (6.53-25.93)	0 (0.0%)	n/a	2.345 (-1.885 to 4.74)	0.155

[c] Independent samples Mann Whitney U test

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The CANTAB PAL is not able to detect differences between people with Down's syndrome who have early stage dementia and those who do not have dementia, as the median values for both outcome measures are the same and the 95% confidence intervals for the median difference include zero.

However, the 95% confidence intervals between the dementia and no dementia groups did not include zero in the K-BIT total raw score and K-BIT verbal subscale, CANTAB SRT median latency, Verbal fluency raw score and Object memory.

I also examined whether there were any differences between the two groups in the CANTAB SRT total correct trials, which can be used as a measure of attention. The mean was 56.93 (SD 32.79) and the median was 59 (range 0-100). There was no significant difference in the Independent samples Mann Whitney U test between the dementia and no dementia groups (p value 0.185, median difference 12 (95% confidence intervals -36 to 8)).

I examined whether there were any differences between the dementia and no dementia groups when using the carer rated assessments. As scores from these tests were also not normally distributed, I used non-parametric statistical tests. Table 3.10 shows these results.

Table 3.10 - Table showing differences in cognitive tests between dementia and no dementia groups – Carer rated assessments

		Dementia			No Dementia			
	N	Mean (SD)	Median (Range)	n	Mean (SD)	Median (Range)	Median difference (95% CI)	P value[c]
BRIEF:								
Shift	11	17.09 (4.21)	16.00 (9-24)	23	15.96 (4.30)	17.00 (8-22)	1 (-2 to 4)	0.445
Inhibit	12	16.92 (3.78)	17.50 (11-22)	23	15.48 (3.96)	15.00 (10-24)	1.5 (-2 to 5)	0.344
Working memory	12	22.75 (5.31)	20.50 (15-31)	23	20.13 (5.23)	21.00 (10-30)	3 (-1 to 7)	0.310
BRI	11	53.73 (10.33)	56.00 (36-66)	23	48.39 (10.86)	51.00 (28-64)	5 (-2 to 12)	0.176
DLD:								
Short Term Memory (STM)	19	8.47 (4.01)	10.00 (0-13)	31	3.00 (3.51)	2.00 (0-13)	6 (3 to 9)	<0.001*
Sum Cognitive Scores	19	26.47 (8.90)	26.00 (7-38)	31	13.23 (10.68)	14.00 (1-37)	15 (8 to 20)	<0.001*
Total Score	19	46.53 (17.35)	43.00 (14-74)	31	26.06 (15.80)	26.00 (2-62)	22 (9 to 31)	<0.001*

[c] Independent samples Mann Whitney U test
*Significant at the 0.05 level

3.5.1 Regression models

In order to determine whether significant differences remained after accounting for age and gender in the relevant ACTB and table top tests, I conducted appropriate statistical models on the cognitive tests that showed a significant difference between the dementia and no dementia groups. Due to the small sample size, I was not able to add any further variables into the model.

The most appropriate statistical models to use were discussed with a statistician (KR).

Table 3.11 - Table showing differences between dementia and no dementia groups in cognitive tests when accounting for age and gender

Measure	N	Model	Estimate used	Estimate (95% CI)	P value
CANTAB SRT median latency	45	Linear regression	Coefficient	391.083 (-13.838 to 796.005)	0.058
Verbal Fluency raw score	44	Negative Binomial	IRR	0.495 (0.272 to 0.901)	0.021*
NAID Object memory	34	Negative Binomial	IRR	0.571 (0.393 to 0.829)	0.003*

*Significant at the 0.05 level

3.6 Concurrent validity

In order to assess concurrent validity, I looked at the strength of correlations between measures that assessed the same or similar areas of cognition. I compared the prefrontal, hippocampal and cerebellar tasks from the ACTB with measures from the table top tests and carer ratings which examined the same cognitive domain. These are shown in Tables 3.12, 3.13 and 3.14.

As the data was not normally distributed, correlations were calculated using Spearman's rank.

Data from those at floor and ceiling is included for all measures, apart from Object memory and Memory for sentences, Tower of London points and Gait assessment where those who did not pass the teaching stage (or, in the case of Gait assessment, those who were not able to mobilise without assistance) are not included in the analysis.

Table 3.12 - Correlation - Prefrontal measures

Measure	CANTAB IED stages completed (p)	CANTAB IED errors block 1 (p)	Modified dots task 2nd stage (p)	Modified dots task 3rd stage (p)	Verbal fluency adjusted (p)	Tower of London stages completed (p)
CANTAB IED stages completed (p)		-0.831 (<0.001*)	0.359 (0.040*)	0.458 (0.007*)	0.422 (0.004*)	0.443 (0.004*)
CANTAB IED errors block 1 (p)			-0.265 (0.136)	-0.317 (0.073)	-0.314 (0.038*)	-0.435 (0.004*)
Modified dots task 2nd stage (p)				0.773 (<0.001*)	0.464 (0.007*)	0.629 (<0.001*)
Modified dots task 3rd stage (p)					0.562 (0.001*)	0.585 (0.001*)
Verbal fluency adjusted (p)						0.479 (0.002)
BRIEF – Shift (p)	-0.050 (0.785)	-0.052 (0.779)	0.014 (0.949)	-0.186 (0.408)	-0.074 (0.689)	-0.205 (0.268)
BRIEF – Inhibit (p)	-0.336 (0.056)	0.366 (0.036*)	-0.133 (0.545)	-0.287 (0.184)	-0.160 (0.374)	-0.535 (0.002*)
BRIEF – Working memory (p)	-0.443 (0.010*)	0.371 (0.034*)	-0.199 (0.364)	-0.220 (0.312)	-0.575 (<0.001*)	-0.574 (0.001*)
BRIEF — BRI (p)	-0.254 (0.160)	0.254 (0.160)	-0.118 (0.601)	-0.302 (0.172)	-0.181 (0.323)	-0.551 (0.001*)

*Significant at the 0.05 level

Table 3.13 - Correlation - Hippocampal measures

Measure	CANTAB PAL stages completed (p)	CANTAB PAL first trial memory score (p)	Object memory (p)	Memory for sentences (p)
CANTAB PAL stages completed (p)		0.860 (<0.001*)	0.354 (0.043*)	0.048 (0.761)
CANTAB PAL first trial memory score (p)			0.345 (0.049*)	0.010 (0.952)
Object memory				0.204 (0.254)
DLD – STM (p)	-0.467 (0.001*)	-0.502 (<0.001*)	-0.572 (<0.001*)	-0.250 (0.107)
DLD – Sum cognitive scores (p)	-0.541 (<0.001*)	-0.574 (<0.001*)	-0.514 (0.002*)	-0.292 (0.057)
DLD – Total Score (p)	-0.468 (0.001*)	-0.532 (<0.001*)	-0.565 (<0.001*)	-0.225 (0.147)

*Significant at the 0.05 level

Table 3.14 - Correlation - Cerebellar measures

Measure	CANTAB SRT median latency (p)	NEPSY visuomotor precision train and car (p)	NEPSY visuomotor precision – car and motorbike (p)	Finger sequencing task (p)	Gait assessment (p)
CANTAB SRT median latency (p)		-0.408 (0.013*)	-0.258 (0.141)	-0.496 (0.001*)	
NEPSY visuomotor precision train and car(p)			0.750 (<0.001**)	0.563 (<0.001*)	
NEPSY visuomotor precision car and motorbike (p)				0.489 (0.004*)	
Finger-nose (p)	-0.479 (0.002*)	0.539 (0.001*)	0.465 (0.006*)	0.441 (0.005*)	-0.558 (<0.001*)
Gait assessment (p)	0.382 (0.021*)	-0.442 (0.010*)	0.456 (0.009*)	-0.296 (0.076)	

*Significant at the 0.05 level

In general, there was correlation between some of the ACTB tests and the table top tests. There was significant correlation of mild to moderate strength between the ACTB tests and the tabletop tests that measured pre-frontal skills and cerebellar function. There was a mild correlation between the ACTB test that assessed hippocampal function (CANTAB PAL) and the NAID Object memory task. Memory for sentences was not correlated with any of the hippocampal tasks.

The ACTB tasks that assessed prefrontal function were not well correlated with BRIEF scores, apart from the working memory subscale. The Tower of London stages completed was much better correlated with BRIEF scores,

although this was only a moderate correlation. All hippocampal measures, apart from memory for sentences were significantly moderately correlated with the DLD scores.

In general, the ACTB has mild to moderate concurrent validity when compared to table top tests and carer ratings that assessed the same domains, although this varies according to brain region and on a test by test basis.

3.7 Summary

50 participants with Down's syndrome were recruited. Of these, 19 had a diagnosis of dementia or possible dementia. Significant differences in age and abdominal circumference were found between the dementia and no dementia groups. Data on feasibility and psychometric properties of the ACTB and table top tests were calculated. The floor and ceiling effects vary from test to test, although the CANTAB IED stages completed and Modified dots task have a very large number of participants at floor.

There were significant differences between the dementia and no dementia groups in scores from the CANTAB SRT median latency, Verbal fluency raw scores and Object memory. Significant differences in CANTAB SRT median latency score did not remain when accounting for age and gender. In general, the ACTB has mild to moderate concurrent validity when compared to table top tests and carer ratings that assessed the same domains, although this varies according to brain region and on a test by test basis.

Chapter 4. Discussion

Chapter 4. Discussion

4.1 Overview

In this chapter, I will summarise my results and comment on them. I will then discuss my findings in the context of other research before commenting on the strengths and limitations of this study. I will go on to discuss the implications of my findings, including my recommendations for what cognitive tests would be useful in an assessment battery for older adults with Down's syndrome. I will conclude by commenting on areas for further research in the field.

4.2 Summary of results

This study assessed the Arizona Cognitive Test Battery (ACTB) against table top tests and carer rated assessments in 50 participants with Down's syndrome. Most participants were able to attempt most of the tasks (between 82% and 90% were able to attempt the ACTB tasks and between 68% and 88% were able to attempt the table top tasks).

Some of the tasks had acceptable numbers of participants that did not fall at the floor or ceiling level. Tests where less than 15% of participants were at floor or ceiling level included the K-BIT total raw score and verbal subscale, CANTAB PAL stages completed, CANTAB SRT, Finger sequencing task, NEPSY visuomotor precision, Tower of London stages completed, Memory for sentences, Finger-nose and Gait assessment. However, some of the tasks had a very high proportion of participants at floor, particularly the CANTAB IED stages completed (53% at floor) and the Modified dots task (76% to 79% at floor).

95% confidence intervals for the median difference between the dementia and no dementia groups did not include zero in only three of the cognitive tasks. These were CANTAB SRT median latency, Verbal fluency raw score and Object memory. When accounting for gender and age, statistically

significant differences remained in Object memory and Verbal fluency raw score. CANTAB SRT median latency approached significance but was no longer significant at the 0.05 level.

The ACTB tests were generally mild to moderately correlated with some of the table top and carer rated tests that assessed similar domains. There was significant correlation of mild to moderate strength between the ACTB tests and the tabletop tests that measured prefrontal skills and cerebellar function (a magnitude of between 0.314 and 0.629 for the prefrontal tasks and, where significant, between 0.382 and 0.539 for the cerebellar tasks). There was a mild correlation between the ACTB test that assessed hippocampal function (CANTAB PAL) and the NAID Object memory task (0.345 to 0.354). Memory for sentences was not correlated with any of the other hippocampal tasks.

The ACTB tasks that assessed prefrontal function were not well correlated with BRIEF scores, apart from the working memory subscale. All hippocampal measures, apart from Memory for sentences were significantly moderately negatively correlated with the DLD scores (with a magnitude from 0.467 to 0.574).

4.3 Interpretation of results

4.3.1 Demographics

The sample included slightly more men than women and more participants with moderate/severe intellectual disability than mild intellectual disability (63% with moderate/severe intellectual disability compared to 37% with mild intellectual disability), although level of intellectual disability was not recorded for all the participants. 28% of the sample were living with family or friends and another 14% in an adult placement, which is very similar to a home environment. The remainder were living in supported accommodation. This reflects the fact that the sample was a community based sample and included participants with a range of level of intellectual disability. There were

no significant differences in gender, ethnic origin or type of accommodation between the dementia and non dementia groups.

This study included a higher proportion of men compared to women in the dementia group (63.2% compared to 36.8%), which differs from what has been seen in a previous study, where more women than men were found to present with cognitive deterioration, although, like in my study, this was not found to be a statistically significant difference (Oliver et al, 1998).

4.3.1.1 Age of study sample

There was a significant difference in age between the dementia and no dementia groups. This is to be expected, as it is well known that increasing age is associated with increasing risk of dementia in the general population (Ballard et al, 2011), and in those with Down's syndrome (Oliver et al, 1998).

4.3.1.2 Generation of study sample

It is important to consider historical context when comparing current research with older adults with Down's syndrome to research with children, teenagers and younger adults with Down's syndrome – not only are there differences in presentation related to age, but there are marked differences in education and health care that these population groups will have received. Alongside this, the skills that society is now promoting are changing. Nowadays, the ability to use computers and the internet and to be able to navigate through an increasingly digital age is, perhaps, starting to be viewed as more important and desirable than the fine motor skills that were required for industry half a century or so ago.

This may therefore influence both formal and informal education and training, with younger generations receiving more training in computer based skills, possibly making them more likely to perform better in computer based assessments.

4.3.1.3 Recruitment

As can be seen in Figure 3.2, there were unequal proportions of people with and without dementia recruited from each geographical area, with some areas not recruiting any participants with dementia and others recruiting more participants with dementia than participants without dementia.

This may be due to differences in how participants were recruited in these localities. Participants with dementia were more likely to have been recruited through psychiatrists, whereas those without dementia may be more likely to have been recruited through day centres. This also highlights differences in local working arrangements and social care, as some areas may have been more likely to move people with higher needs out of the area whereas other teams may have been able to support them within the local area. Alongside this, local clinical policies and practice may mean that some teams are more likely to discharge patients with Down's syndrome who do not have any active health concerns and others may not.

4.3.1.4 Physical health

Physical health problems were prevalent in the total sample, with 41% of participants having a thyroid problem and 18% having epilepsy. As dementia of Alzheimer's type in Down's syndrome is associated with epilepsy, it is not surprising that the percentage of people with dementia who had epilepsy was higher than those who did not have dementia (26% versus 13%), although this difference did not reach statistical significance.

Interestingly, there were fewer people in the dementia group who had a family history of dementia as compared to the no dementia group, although this was not a statistically significant difference. Data on family history were only available from 33 participants and it may be that paid carers were not always fully aware of detailed family history when answering this question.

Average (median) pulse and diastolic blood pressure in the whole group was lower than the general population. This is a well known feature of Down's syndrome, and, interestingly, low blood pressure has previously been suggested as a possible link to Alzheimer's disease in people with Down's syndrome (Morrison et al, 1996).

There was a statistically significant difference in abdominal circumference between the two groups, with those with dementia having a smaller abdominal girth. The median weight for the dementia group was 64.9kg and in the no dementia group it was 82.6kg. There was no statistically significant difference in weight between the two groups, however the sample size for this variable was small (n=25). In the general population, midlife obesity has been found to be a risk factor for Alzheimer's disease (Ballard et al, 2011), although as the course of dementia progresses, people with dementia are more likely to develop feeding difficulties and subsequent weight loss.

4.3.1.5 Mental health

Mental health problems were prevalent in this study, with 15.2% of participants having a history of psychosis and 32.6% of participants having a history of depression. There were higher percentages of people with psychosis and depression in the no dementia compared to the dementia group, although this was not a statistically significant difference.

These rates are much higher than epidemiological studies predict, although a recent Scottish study identified a higher prevalence of mental ill health in adults with Down's syndrome aged 45 and over compared to those aged 16-44 (31.2% compared with 18.3%) (Mantry et al, 2008). The higher rates of mental illness in my study sample may be due to higher rates of mental illness seen in older people with Down's syndrome (perhaps related to a reflection of behavioural changes seen in pre-clinical dementia). Alternatively, it may be explained by the fact that the majority of recruitment was through intellectual disability teams, and often through intellectual disability psychiatrists. It is likely that intellectual disability psychiatrists discharge

patients who do not have mental illness and are therefore more likely to recruit either people with dementia or those with other mental illnesses, such as psychosis or depression.

Interestingly, there was also no significant difference between the dementia and no dementia groups when comparing possible organic condition as identified by the PAS-ADD checklist. This may be because of the small sample size in this group, as 22.2% of participants with dementia scored above the threshold for possible organic condition as opposed to 12.9% in the no dementia group. Alternatively, it may be because the PAS-ADD checklist asks about symptoms in the previous 4 weeks, so if symptoms of dementia were present but had not progressed over the previous 4 weeks, they are unlikely to have been detected using the PAS-ADD checklist. Furthermore, the PAS-ADD checklist is a screening tool rather than a diagnostic tool and only includes 6 questions related to symptoms of organic disorders, which may not be sensitive enough to detect a significant difference.

4.3.1.6 Generalisability of study sample

This study sample can therefore be said to be representative of a population of older adults with Down's syndrome known to Intellectual Disability Psychiatry Services and living in a community setting in England. Given the age, location and methods of recruitment of the study sample, it is important to be cautious when comparing results to studies conducted with participants of a younger age, living in a different country or residential setting or recruited in a different way. The generalisability of this study could have been increased by recruiting from sites outside Greater London and the surrounding counties and using different recruitment channels (e.g. recruiting through charities and support groups as well as local Intellectual Disability Services).

4.3.2 Feasibility

4.3.2.1 Number of participants attempting the tasks

The majority of participants were able to attempt the majority of the tasks. A larger proportion of participants attempted the ACTB tasks as compared to the table top tasks and a larger proportion of the no dementia group were able to attempt the tasks as compared to the dementia group.

The order of the tasks was counterbalanced to reduce position effects of the tasks; however, as the study was designed to assess the use of the ACTB, where participants were not keen to attempt all the tasks, I focussed on encouraging them to attempt the ACTB tasks. Alongside this, a number of the table top tasks were associated with teaching stages. If participants failed to pass the teaching stage, they did not continue with the task. The ACTB had a general training task – the CANTAB MOT, however, whilst a number of participants were able to pass the CANTAB MOT, this did not help teach or assess their abilities for each individual computer based task. These two reasons may go some way to explaining why slightly more participants were able to attempt the ACTB tasks compared to the table top tasks. Of course, another reason may be that the computer based tasks were more popular and/or easier to use.

When considering feasibility, it is important to note that the assessment session took approximately 2-3 hours. Although breaks were given and, on occasion, second and third assessments were arranged, the requirements to concentrate and pay attention to the tasks were sometimes difficult for participants. It may be that participants did not have any previous experience with completing tasks in this manner before and some were likely to be unfamiliar with the concept of testing, with limited or no previous exposure to or schooling or examinations.

Therefore, attention and concentration levels and degree of exposure to previous cognitive testing were likely to have had an effect on whether the tasks were attempted.

The CANTAB SRT total correct trials provided a measure of attention. There was no significant difference in this score when comparing the dementia and no dementia groups. However, this task may not have had satisfactory validity or been sensitive enough to detect differences in attention levels. It would be useful to consider adding a measure of attention into future cognitive test batteries as, subjectively, there appeared to be limited attention in a number of participants both with and without dementia.

4.3.2.2 Choice of outcome measures

Previous research using the ACTB in people with Down's syndrome has reported the mean and standard deviation (SD) when reporting outcome measures (Edgin et al, 2010a). However, the data in this study did not fit a normal distribution, and much of the data was skewed. This is likely to be related to cognitive weaknesses in this group, resulting in large numbers of participants at floor for a number of outcome measures. I have therefore reported mean and standard deviation as well as median and range for the relevant outcome measures.

Another consideration when comparing to previous research is that a number of different outcome measures are available for some of the cognitive tests, particularly the computer based tests, where, for example, in the case of the CANTAB PAL, up to 21 different outcome measures are available. Although this is designed to be a quality of these tests, when a large number of participants perform at floor, several of the outcome measures become invalid as they rely on participants completing some or all levels of the task. There is therefore a risk that non-valid measures are used, or that multiple statistical analyses are conducted using a variety of different outcome measures for the same test. When conducting my analyses, I selected a

limited number of outcome measures that were valid and applicable to my study sample, as described in Section 2.9.2.

Three of the assessment tools are designed to be transformed to percentiles using population norms. These are the K-BIT II, NEPSY visuomotor perception and BRIEF scores. In the case of the NEPSY and BRIEF, the population norms are for children and therefore raw scores only were used in my analyses. In the case of the K-BIT, most of the participants in my sample would have been at the floor of the population norms (the floor for K-BIT II is an IQ of 40, and the K-BIT II appears to score lower than other popular psychometric tests for IQ). I have therefore used K-BIT II raw scores in my analysis, which had a good spread of measures in the study sample and reflects other research in the field (Edgin et al, 2010a).

4.3.3 Difference between dementia and no dementia groups

4.3.3.1 Floor and ceiling levels and distribution of data

Tables 3.7, 3.8, 3.9 and Appendix tables A. 2, 3 and 4 show the floor and ceiling levels of the tasks and compare these in the dementia and no dementia groups. A number of tests had relatively acceptable floor and ceiling levels and a reasonable spread of results. These were K-BIT total raw score and verbal subscale, CANTAB PAL stages completed, CANTAB SRT, Finger sequencing task, NEPSY visuomotor precision, Tower of London stages completed, Memory for sentences, Finger-nose and Gait assessment. I used a fairly low threshold to determine floor and ceiling levels, however the original research on the ACTB was more stringent (Edgin et al, 2010a).

A large proportion of participants both with and without dementia (37.8%) were at floor for the CANTAB first trial memory score, which was the outcome measure I based by power calculation on. Very large proportions of participants were at floor of the ACTB prefrontal tests (the CANTAB IED stages completed and the Modified dots tasks). 43.8% of people with dementia were at floor of the Tower of London points and for the Object

memory task, although these figures also included those who did not pass the teaching stage.

When floor and ceiling levels are stratified according to dementia status and level of intellectual disability (see Appendix tables A2, 3 and 4) it can be seen that for some but not all cognitive tests, a higher proportion of those with dementia and moderate intellectual disability are at floor compared to those with dementia and mild learning disability. When interpreting these results, it is important to be aware that data on level of intellectual disability was missing for 15 participants and therefore n is only a maximum of 35. When n is low, small differences in real numbers can have a large influence on percentages, which may explain why for some outcome measures more participants with mild intellectual disability were at floor compared to those with moderate intellectual disability.

4.3.3.2 Differences between dementia and no dementia groups

Non parametric methods were considered in the absence of suitable transformations of the data. These are less sensitive to extreme values, but are also potentially less robust, as they rely on ranking of the data rather than the raw values of the data. Estimates (mean and median) and 95% confidence intervals are presented in order to indicate the magnitude of the difference. As this was an exploratory study, and analyses were not adjusted, significant p values should be interpreted with caution.

95% confidence intervals for the median difference did not cross zero in only CANTAB SRT median latency, Verbal fluency raw score and Object memory. Of these, when accounting for gender and age, statistically significant differences were found in Object memory and Verbal fluency raw score.

In this study, of the 12 cognitive tests that were evaluated, only 3 were found to detect differences between the dementia and no dementia groups and only one of these tests was from the Arizona Cognitive Test Battery. This is

unusual, as we would have expected more cognitive differences to be detected between the dementia and no dementia groups.

Therefore, in answer to my hypotheses, the ACTB has not been shown to clearly detect differences between people with Down's syndrome who have early stage dementia and those who do not have dementia. This study also did not identify many specific differences in the neuropsychological profiles of people with Down's syndrome who have dementia and those who do not have dementia, with few tests identifying significant differences between the two groups.

In general, therefore, we can say that either this study does not have enough power to determine differences between the dementia and no dementia groups in the majority of cognitive tests, or that the majority of tests used in this study do not pick up differences between the two groups.

An alternative explanation may be that the no dementia group is, in fact, a group that is already in the process of developing a cognitive decline that has not yet been ascertained clinically. The similarities in the results of the cognitive tests may therefore reflect underlying similarities between the two groups. In fact, research with older adults with Down's syndrome, has shown that early changes in personality and behaviour followed by an increase in frontal lobe characteristics and/or a deterioration in memory is seen prior to the development of full Alzheimer's disease (Ball et al, 2006a).

Based on these findings, I would therefore suggest that although it may be useful to use a cognitive test battery in older adults with Down's syndrome when tracking changes over time, it may not be particularly useful for differentiating between those with and without dementia. In this case, it may be more helpful to focus on using specific tests that identify specific cognitive skills, although further research is required to confirm which cognitive skills deteriorate later in the course of dementia.

4.3.4 Concurrent validity

4.3.4.1 Prefrontal function

There was significant correlation of mild to moderate strength between the ACTB tests and the tabletop tests that measure prefrontal function. The ACTB tasks that assessed prefrontal function were not well correlated with BRIEF scores, apart from the working memory subscale. The Tower of London stages completed was much better correlated with more of the BRIEF subscales. This implies that the ACTB has mild to moderate concurrent validity with some of the other measures of prefrontal function, but that the Tower of London may have better concurrent validity, given that it correlates with both the ACTB tasks and the BRIEF. It is not clear, however, how valid the BRIEF is in this population, as it was designed for use in children and a number of cases were omitted from analysis due to incomplete datasets or high scores on negativity and inconsistency measures.

4.3.4.2 Hippocampal function

There was a significant mild correlation between the ACTB tests that assessed hippocampal function and the NAID Object memory task, but there was no significant correlation between Memory for sentences and any of the other hippocampal tasks. All hippocampal measures, apart from Memory for sentences, were moderately correlated with the DLD scores.

Memory for sentences did not correlate with any other hippocampal tasks or carer rating scales, thus suggesting that either this is not a good test of hippocampal function, or that this utilises a different neural network. This is highlighted in the difference between verbal and visuospatial memory as described in section 1.4.6.1.1.

4.3.4.3 Cerebellar function

The ACTB cerebellar tasks were mild to moderately correlated with the relevant table top tasks. Apart from the NEPSY visuomotor precision, these tasks mainly assessed cerebellar motor function rather than cerebellar cognitive function and until we have a better understanding of how to accurately measure cerebellar cognitive function, it is difficult to fully comment on how valid these tasks are in assessing cerebellar cognitive function. Nevertheless, some cerebellar tests appear to have good feasibility and are able to show differences between those with and without dementia.

Regarding my secondary hypotheses, the ACTB has been shown to have mild to moderate concurrent validity when compared to table top tests and informant ratings, although this varies according to brain region and on a test by test basis. A number of tests had relatively acceptable floor and ceiling levels and a reasonable spread of results, however some had very high numbers of participants at floor.

4.4 Results in the context of other research

4.4.1 Cognitive function in children and adults with Down's syndrome

4.4.1.1 Executive function

Similar to Pennington's study comparing cognitive function in school aged individuals with Down's syndrome to mental age matched controls (Pennington et al, 2003), I did not find differences in non verbal tests of executive function when comparing two groups (although Pennington's study compared those with Down's syndrome to mental age matched controls and in my study, I compared dementia and no dementia groups). The only executive function test that showed a difference between the two groups in my study was Verbal fluency, giving further credibility to Jarrold et al.'s comment that it may be that the modality in which information is recalled (i.e. verbal vs. non-verbal) moderates the results (Jarrold et al, 2008). It may be

that verbal measures of pre-frontal function better differentiate dementia from non-dementia cases than non-verbal tasks.

However, the lack of significant differences between the groups may also be due to floor effects. The means of the Modified dots task were lower than the means of the same tests in the original ACTB paper, which is likely to be a reflection of the lower cognitive abilities of the sample in my study. This is confirmed by the lower mean K-BIT raw scores in my study compared to that in the ACTB paper. It may be that this lower cognitive ability is due to cognitive decline with age, although this study was not designed to address this question.

4.4.1.2 Long term memory

When comparing the CANTAB PAL first trial memory score results in my study to that in the original ACTB study, the mean was much lower in my study (2.22 compared to 7.42), which is likely to be a reflection of the differences in memory related to the difference in ages of people with Down's syndrome in the two studies. The standard deviation and range were smaller in my study compared to the original ACTB paper, which may be a result of the more diverse range of ages and associated cognitive changes in the original ACTB paper (7-38 years, compared to 45-67 years).

Notably, the spread of the results in my dataset were not normally distributed. Also, the percentage of participants at the floor of the CANTAB PAL first trial memory score was much higher in my study (37.8% versus 14.1%).

4.4.1.3 Cerebellar function

There are few studies of cerebellar cognitive function in people with Down's syndrome. When comparing the distribution of the data of the CANTAB SRT median latency and NEPSY visuomotor precision train and car in my study to the original ACTB study, participants in my study showed poorer performance. This highlights what is already known about decline in fine

motor skills with age in Down's syndrome. The original ACTB paper does not report NEPSY visuomotor precision scores for car and motorbike and reports a different outcome measure for Finger sequencing and I was therefore not able to compare them.

As cerebellar cognitive skills are thought to include executive function and working memory, some of the tasks in the battery, particularly those that assess prefrontal functions, are also likely to assess cerebellar cognitive function.

4.4.2 Cognitive function in adults with Down's syndrome and dementia

This study, like other studies with people with dementia of Alzheimer's type and Down's syndrome showed impairment of memory in people with dementia (Deb et al 2007a; Devenny et al, 2000). In my study, this was demonstrated by poorer performance in the Object memory task. Unlike Devenny's study, my study was not able to show differences in cognitive decline with increasing severity of dementia as participants were not categorised according to level of severity of dementia. It is likely that the majority of my participants had mild dementia, given that those with more severe dementia would not have been able to attempt the tests and were therefore not recruited.

In Ball et al's study, which assessed 103 people with Down's syndrome aged 36-72 (including a group of 25 people with Dementia of Alzheimer's type), significant differences were found between the dementia and no dementia groups on all 12 measures, using ANCOVA and taking into account age and level of intellectual disability (Ball et al, 2008). These included tests of executive function and memory, including Tower of London, Verbal fluency, Object memory and Memory for sentences. In my study, I also found a statistically significant difference comparing the dementia and no dementia groups on Object memory and Verbal fluency, but I did not identify significant differences in the Tower of London or Memory for sentences tasks.

A sub-set from the previous study who do not have a diagnosis of dementia of Alzheimer's type are further described in Ball et al (2010) and the mean and range of the cognitive tests used are given. When comparing scores to my sample of participants in the no dementia group, the mean of Verbal fluency is very similar, the mean for Memory for sentences in my study is slightly lower and the mean for Object memory for my study is slightly higher.

In her study, Ball identified behavioural disinhibition and apathy and in pre-clinical dementia in people with Down's syndrome (Ball et al, 2010). Alongside this, Adams and Oliver identified that participants with Down's syndrome and cognitive deterioration showed decreases on measures of executive function and significant changes in behaviour even at the early stages of cognitive deterioration (Adams and Oliver, 2010). The sample group in my study is older, and those in the no dementia group may already have some of the changes in executive function and behaviour seen in the early stages of cognitive deterioration. This may explain why so many participants, including those in the no dementia group, performed at floor for a number of the executive function tests.

Although this study was not designed to measure attention in older people with Down's syndrome and dementia, it became evident during the course of data collection that a number of participants were not able to attempt or complete the tasks. At times this was due to limited attention. This seems to differ from cognitive testing in younger people with Down's syndrome, where studies have been able to assess cognitive function over a similar assessment time and in more demanding situations, such as during MRI scanning or ERP testing.

Although there were no statistically significant differences between the dementia and no dementia groups in the CANTAB SRT total correct trials (the outcome measure from the SRT which can be used as a measure of attention), the median score was 59 out of a possible total score of 124, which is fairly low for a task of relatively low cognitive demand. Das et al found that older adults with Down's syndrome performed more poorly on

cognitive tasks, particularly those that required planning and attention when compared to older adults with intellectual disability not due to Down's syndrome and younger adults with intellectual disability both with and without Down's syndrome (Das et al, 1995). Krinksy-McHale et al (2008) have suggested the addition of a selective attention task (a paper and pencil picture cancellation task) to a neuropsychological battery for dementia in Down's syndrome and have found that changes in performance can be observed approximately 2 years before a clinical diagnosis of dementia.

Like the findings in Deb's qualitative study (Deb et al, 2007a), in my study I also noticed that participants were generally slow. This is reflected in the long median latency times seen in the CANTAB SRT, and may also have contributed to slowness of initiation in other cognitive tasks.

4.5 Strengths

This is the first study to fully assess the use of the ACTB in older adults with Down's syndrome and compare its use in those with dementia to those without dementia. The study was designed to be pragmatic so that results could be directly applied to this population. It used manualised standardised assessments of cognitive skills in 50 adults with Down's syndrome. As the primary researcher, I was a trainee in the Psychiatry of Intellectual Disability and thus had experience working with people with intellectual disabilities, including in assessing capacity and making information accessible. I also attended training on use of the CANTAB and the ACTB.

Dementia or possible dementia cases were clarified by consensus opinion, using medical information collected at assessment and from clinical teams.

Statistical analyses were hypothesis based and limited to specific statistical tests that were relevant to the research question, thus reducing the possibility of multiple analyses and type I errors. Statistical analyses were conducted in consultation with an experienced medical statistician.

4.6 Limitations

There are a number of limitations to this study, which mainly arise from the logistical issues of working with this demographic population. I will discuss them below.

4.6.1 Sample size

This study was initially powered to detect an effect size of 0.74, at 80% power and with a 5% overall significance level. This calculation was based on the mean and standard deviation of the CANTAB first trial memory score, which was taken from the original ACTB paper (Edgin et al, 2010a).

The CANTAB PAL first trial memory score had a very different mean and SD in this study compared to that in Edgin's study. It also had a large number (37.8%) of participants at floor and was therefore not the preferred outcome measure for use in this population.

When interpreting the results, we therefore have to be aware of the possibility of this study being underpowered and the subsequent possibility of type II errors (i.e. false negatives). Although sample size is a limitation, it only relates to the analyses examining the differences between the two groups. Data on feasibility and concurrent validity of the tests should not be affected by the sample size. The sample size is comparable to several other studies of cognitive skills in this population group.

4.6.2 Confounding factors

There are a number of confounding factors that may have influenced the results.

In the general population, age and gender are known to be related to dementia. Where relevant, these were accounted for using statistical models. Level of intellectual disability is also likely to affect scores on cognitive tests. However, as I was not able to obtain a full data set for this variable, I was unable to account for this in the analyses, as this would have narrowed down the sample size even further.

There are several other factors that may have influenced performance, including mental and physical health, sensory impairments and medication. I was not able to account for these in secondary analyses due to the small numbers in the study. However, in my initial analysis I did not find many significant differences in mental and physical health conditions when comparing the dementia and no dementia groups.

Other factors such as the timing of assessments and location may have also possibly confounded results and it is important to consider this when interpreting the results. However, seeing most participants in a familiar environment is arguably a strength as it allowed them to perform at their best, free from the distractions of an unfamiliar environment. I tried to be as flexible as possible, allowing participants to stop and continue on another occasion if required, in order to ensure that each participant performed as well as they could.

There may also be other hidden confounders or mediators that I am are not aware of or have not considered.

4.6.3 Dementia diagnosis

Participants were categorised into either a "dementia" or "no dementia group". This categorisation was done in consultation with treating clinicians and with my primary supervisor. In most cases, diagnosis (or lack of diagnosis) was clear cut, but in some cases, participants were said to have possible dementia. They were included in the dementia group.

There continues to be a lack of clinical consensus in the diagnosis of dementia in people with Down's syndrome and there is a chance that clinical dementia diagnosis was not consistent amongst the sample. However, it has been shown that a clinical diagnosis of dementia is just as reliable, if not more so, than manualised criteria (Sheehan, personal communication). There are also likely to be participants in the no dementia group who will move into the dementia group over time. It is therefore important to remember that the dementia/no dementia groups were used in order to answer the research question but are somewhat transient. It may be more useful to consider the no dementia group as a pre-clinical dementia group in this age group.

4.6.4 Down's syndrome diagnosis

Participants were recruited through intellectual disability teams, care homes and day centres. Most people presented with classical facial features of Down's syndrome, but features were more distinctive in some compared to others. Most participants and clinical teams did not have results of a genetic diagnosis available and therefore a diagnosis of Down's syndrome was accepted if the researcher was told by the referring person (i.e. learning disability team, day centre or care home staff) that the participant had Down's syndrome.

Participants in this study therefore do not have genetic confirmation of Down's syndrome and it is not possible to report on differences between those with a full trisomy and those with a translocation or mosaicism.

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4.6.5 Assessment procedures

The assessment was designed to be undertaken in one session if possible, with timing carefully considered so as to obtain as much useful and relevant information as possible to answer the research question and to avoid long and tiresome assessments for the participant and their carers or relatives.

In some cases, the attention and concentration of participants was limited, which made carrying out the full assessment in accordance with the manual challenging.

Participants' attention may have fluctuated during the course of the assessment; some participants became more tired during the course of the assessment, although others settled in to the testing process and became more engaged as the assessments progressed. In order to account for position effects of the tests, the battery was counterbalanced after 26 participants had been recruited.

4.7 Implications of results

This study shows that particular tests, be it from the ACTB, table top tests or carer ratings are feasible to use and have mild to moderate concurrent validity when used in older people with Down's syndrome. A few of the tests showed differences between the dementia and no dementia groups. However, most tests did not detect differences between the two groups.

These tests are likely to have some value when assessing cognitive skills in both research and clinical practice. When using these tools, researchers and clinicians need to be aware of possible confounding factors and take these into account when conducting the tests and when interpreting the results.

4.7.1 Type of test used

Computer based, table top and carer rated tools can all be used to assess cognitive skills in older people with Down's syndrome. They each have their advantages and disadvantages, which I will discuss below. If possible, it may be preferable to use all three methods in order to triangulate data.

4.7.1.1 Computer based tests

Computer based tests can generate a large amount of data from a relatively simple cognitive paradigm. As errors can be measured, an error rating can sometimes be used as an outcome measure to overcome the problem of high floor levels.

The CANTAB tests in particular have been extensively used in a number of populations and are becoming increasingly used in people with Down's syndrome. Training and specific hardware and software requirements make the tests well standardised and less likely to be modified, making them suitable for use at times when standardisation is very important, for example in clinical trials. Data is generated in a formatted spreadsheet, making subsequent analyses less onerous.

However, the CANTAB tests have not specifically been designed for people with intellectual disability and the tests are often abstract and may not be that engaging for this population group. For example, the graphics are very basic compared to current computer games, the patterns are sometimes small and difficult to see (e.g. a blue pattern on a black background) and the sound effects are monotonal.

The two other computer based tests used in this study – Modified dots task and Finger sequencing task – were developed by the Down Syndrome Research Group, University of Arizona. They were specifically designed to be engaging tasks for this population group and use cartoons and more colourful graphics and a more engaging variety of sounds. They have been validated,

but are not in common use and it remains to be seen whether they will continue to be used in this population group, as they may place more of a technical demand on the researcher. For example, a number of outcome measures from the Finger sequencing task require two researchers to assess (one to encourage the participant and one to count the number of valid finger taps), and even with two researchers it can be difficult to score.

The tests included in the Arizona Cognitive Test Battery (ACTB) have been selected or designed for people with Down's syndrome and therefore do not require verbal responses, thus limiting the load required for verbal memory and reducing this as a confounding factor.

Researchers and clinicians need to be cautious of the wide variety of outcome measures generated by several of the computer based assessments, as some of them may not be valid or applicable if many participants do not complete all the levels. Some of the computer tests require the purchasing of specific hardware and software which can make research costs quite expensive and may rule out their use in the clinical setting.

4.7.1.2 Table top tests

These are easier to administer and some have been specifically developed for use with people with intellectual disability. They often only generate one or two outcome measures. Due to the nature of these tests, they can be easier to modify/adapt according to the needs of the participant although this also means that they are at more risk of being less standardised. In this respect, they might be more appropriate for use in clinical cognitive assessments.

Most table top tests used in this study had minimal cost, although some, such as the Tower of London test have high initial costs, due to the purchase cost of the materials.

4.7.1.3 Carer rated assessments

Carer rated assessments are easy to administer and score. They are therefore less time consuming than the computer based and table top cognitive tests. Some, such as the DLD, have been specifically developed for people with intellectual disability, and are already well used in research and clinical practice.

They provide second hand information of cognitive functioning and the quality of information given depends on the quality of the relationship between the rater and the person with intellectual disability.

The DLD is widely used in both research and clinical practice, and is easy for carers to complete and for researchers to score. The BRIEF has a number of statements that may not be applicable to people with intellectual disability (e.g. "does not check work for mistakes") and is more time consuming for researchers to score.

Carer rated assessments may be best used alongside participant based tasks. However, they may be a good substitute for participants who perform at floor for a number of cognitive tests. Response rates are likely to be higher. Applicable carer rated assessments such as the DLD are a valuable addition to cognitive testing, however further development regarding identifying subsections of the tools and whether they can assess specific cognitive skills are likely to provide more information to the researcher.

4.7.2 Recommendations for test battery

The main aim of this study was to assess the use of the ACTB in older adults with Down's syndrome and establish its validity in testing for dementia. However, as the ACTB is an assessment battery, there is potential for variation in the feasibility and validity of each individual task. Based on the findings of this study, I have made some suggestions regarding which of the tests in this battery are most useful when assessing cognitive skills in older people with Down's syndrome. I suggest that a combination of computer based tests, table top tests and carer rated assessments are useful when assessing cognitive skills in this population. Together they have different strengths and limitations as described in the previous section and therefore a combination should hopefully allow to play to the strengths of each test while minimising the limitations. In Table 4.1 I have detailed the tests from this study that I would recommend are included in a cognitive test battery for older people with Down's syndrome.

Table 4.1- Recommended cognitive tests to use in a cognitive test battery for older people with Down's syndrome.

Test	Outcome measures	Comments
K-BIT II	-Total raw score - Verbal subscale	Able to detect differences between dementia and no dementia groups. Easy to administer. Used in other studies.
CANTAB PAL	- Stages completed	Used in many similar studies
CANTAB SRT	- Median latency - Total correct trials	Median latency assesses cerebellar function and is able to detect differences between dementia and no dementia groups. Total correct trials assesses attention
Verbal fluency	- Raw score	Able to detect differences between dementia and no dementia groups. Easy to administer. Used in other studies.
Tower of London	- Stages succeeded on	Easy to administer. Used in many other studies.
NAID Object memory		Able to detect differences between dementia and no dementia groups. Easy to administer. Used in other studies.
DLD	- Sum of cognitive scores - Total score	Able to detect differences between dementia and no dementia groups. Easy to administer. Used in many other studies.

4.8 Future research in the field

4.8.1.1 This study

This study feeds in to a larger study looking at individual differences in the cognitive profiles of people with Down's syndrome, run by the LonDownS consortium (www.ucl.ac.uk/londowns/). The LonDownS consortium aims to further understand dementia in people with Down's syndrome using a multidisciplinary approach.

The size of the LonDownS study should overcome the problems with sample size that I encountered in my study. The greater numbers of participants that are planned to be recruited into the LonDownS consortium study should also allow for more variables to be controlled for in data analysis (in particular, level of intellectual disability and possibly level of severity of dementia).

Genotyping from participants will help further understand genetic risk and protective factors for specific cognitive skills and deficits. Participants may also be invited to donate a few hair samples in order to grow stem cells, to understand underlying pathology on a cellular basis.

It is hoped that some participants will also be able to participate in an EEG based ERP (Event Related Potential) study, which will allow for further understanding of the electrophysiological changes associated with cognition in this group.

4.8.1.2 Other research

Collaborative and interdisciplinary working is likely to further neuroscience research at a faster rate. Alongside looking at clinical cognitive assessments (which are valuable, but have limitations, as described previously), research examining how the brain is working during cognitive testing is also likely to be highly beneficial.

This includes neuroimaging studies (including MRI and PET), electroencephalography (including ERP based paradigms) as well as genetic, cellular and animal studies.

Rather than thinking about cognitive deficits in terms of location (ie. prefrontal, hippocampal and cerebellar), it may be more useful to think about them in terms of specific skills (eg. working memory, visuo-spatial long term memory etc), as it is likely that more than one area of the brain is involved in each function. This is reflected in our understanding of neural networks, for example, visuo-temporal attention requires an intact cerebellum, suggesting that the cerebellum plays an important role in this neural network (Keren-Happuch et al, 2012).

There is a lack of research on cerebellar cognitive function in people with Down's syndrome, including older adults with Down's syndrome. It would be important for cognitive research, alongside functional imaging and animal studies to examine this. There is also more research required to understand attention and whether (and if so, how) this changes with age and/or dementia in people with Down's syndrome.

Whilst it is well established that people with Down's syndrome have a much higher rate of dementia than those in the general population, it is still not clear why some people with Down's syndrome will develop dementia and others do not appear to develop the clinical signs of dementia. We are aware of a few genetic risk factors, such as APO-E (Prasher et al, 2008) and PICALM, (Jones et al, 2013), but there is further work to be done regarding identifying risk and preventative factors. If we can further understand this question, it may go some way to helping our understanding of dementia in the general population.

At present, there are a number of individuals, research groups and collaborations working on research in cognitive deficits in with Down's syndrome, from mouse studies and cellular studies to clinical trials. The challenge to the research community is how to coordinate current and future

research so that findings are easily disseminated and translated to clinical practice.

4.9 Conclusion

Some tests in the ACTB test battery appear to be feasible and valid in older adults with Down's syndrome, although they did not clearly identify differences between those with dementia and those without dementia. Table top tests have also been shown to be feasible and valid, although they vary on a test by test basis. Specific table top tests (such as Object memory) may be better at detecting differences between those with and without dementia, although it may be that there are few differences in specific cognitive skills between the two groups, and it may be more useful to consider older adults with Down's syndrome without a diagnosis of dementia as a pre-clinical group.

The assessment battery used in this study may be helpful in assessing cognitive skills and cognitive decline in older people with Down's syndrome, however it may be of limited value in those who have a diagnosis of dementia. It would be helpful to include an assessment of attention in any cognitive battery used in older adults with Down's syndrome.

Research is moving away from a dementia/no dementia dichotomy and perhaps moving towards dementia as a final outcome on a continuum. Therefore, assessments of specific cognitive skills, perhaps using some of the assessment tools examined in this study may contribute to future research from epidemiological studies to clinical trials, as well as having a clinical application.

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Appendix

File Copy

North Wales Research Ethics Committee - West
Bangor
Clinical Academic Office
Ysbyty Gwynedd Hospital
Betsi Cadwaladr University Health Board
Bangor
Gwynedd
LL57 2PW

Tel/Fax:: 01248 -384.877

Dr Andre Strydom
Department of Mental Health Sciences
Charles Bell House, 2nd Floor
67-73 Riding House Street,
London
W1W 7EJ

16 December 2011

Dear Dr Strydom,

Study title:	**Assessing specific cognitive deficits associated with dementia in older adults with Down's syndrome: a London based study**
REC reference:	**11/WA/0369**
Protocol number:	**11/0521**

The Research Ethics Committee reviewed the above application at the meeting held on 15 December 2011. The Committee wishes to thank you, and your research team, for attending via speakerphone to discuss the study.

Ethical opinion

Ethical issues raised by the Committee in private discussion, together with responses given by you when contacted

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

i) The Committee noted that the protocol does not present a theoretical argument for conducting a DNA analysis in this study.
You clarified that DNA samples will be analysed to establish whether there is a correlation between a genotype and a specific phenotype in people with Down's syndrome and dementia.

ii) The Committee queried whether the team has considered the medication (which would be taken by the majority of the potential participants) as a confounding factor in the study.
Dr Sinai clarified that excluding people who are medicated would dramatically reduce the potential sample size and therefore the team has chosen to make a note of the medication taken by the participants and account for it as a confounding factor. This may also make an interesting secondary analysis.

iii) The Committee queried the reason for measuring participant's blood pressure.
You clarified that pulse, blood pressure, height and weight will be measured as important indicators of general health, which could yield data of potential impact on dementia and cognitive function.

iv) The Committee queried whether the results will be influenced by the fact that the Arizona battery has been validated for use in a younger age group than the one for which the team intends to use it. You clarified that this is one of the main reasons for conducting the study, to establish whether this is a useful and reliable tool, and whether its scores would correlate with results of other measures (such as the dementia scale for people with learning disabilities (DLD), and available clinical information. It would also enable to tailor the test for the specific needs of this population and produce and optimised version (e.g. if it was found to be too long or people were getting tired).

v) The Committee requested a clarification of the proposed method to send the samples by post. Dr Sinai clarified that it is unlikely that this will happen as it would be preferred that the Investigator collects the samples and takes them to the laboratory; however, should it prove difficult to obtain a sample at the time, a postal pack will be left with participants.

vi) The Committee requested a clarification regarding the specimen disposal: the answer provided to the question 13 in part B section 5 of the application form states that DNA is not relevant material for the scope of the Human Tissue Act. The Committee acknowledged that this is correct, however, the sample taken contains buccal epithelial cells and these will need disposing of in accordance to the provisions of the Act, unless they are held under a licence. Dr Sinai clarified that blood, saliva and buccal epithelial cells will be stored and processed in batches of 25 samples (this may take 6 months to 1 year). The Committee confirmed that batch processing is perfectly acceptable, but that the team will need to ensure that either the sample is processed completely so there is no residual cellular material to store, or arrangements are made for it to be disposed at the end of the project. Dr Sinai confirmed that it will be destroyed at the end of the project.

The Committee concluded that the research design and the proposed analysis were deemed suitable for answering the research question. No further ethical issues were raised.

Care and protection of research participants; respect for participants' welfare & dignity; data protection and participants' confidentiality

i) The Committee requested a clarification of the procedures in place should a participant who has not been diagnosed with dementia score above the threshold on the cognitive assessment test. You clarified that they would be referred to the clinical team, who will then take the appropriate action.

ii) The Committee requested a clarification of the proposed home visits for cognitive testing and queried whether this is an appropriate environment. Dr Sinai clarified that the testing will take place either at home or at community LDT locations and the sponsor requested that the team make arrangements to ensure a career is present. The UCL Lone Worker Policy will apply.

iii) The Committee requested a clarification of the proposed gift to be offered to participants and whether it is appropriate or should it be replaced by money?
You clarified that this was thought out carefully and consideration was given to gift vs. token issue; it was agreed by the research team that since the majority of the participants many not have capacity or competence and may not understand the value of £20 or how to choose an item from a shop – however, participants may be given a choice between a gift or a gift voucher.

No further ethical issues were raised

Informed Consent process
The Committee noted that written informed consent is taken as part of a process - with participants having adequate time to consider the information, and opportunity to ask questions. The information is clear to what the participant consents and there is no inducement or coercion.

Compliance with the Mental Capacity Act (England and Wales) 2005

i) Relevance of the research to impairing condition
The Committee agreed that the research is connected with an impairing condition (dementia, Down's syndrome) affecting persons lacking capacity, or with the treatment of the condition.

ii) Justification for including adults lacking capacity to meet the research objectives
The Committee agreed that the research could not be carried out as effectively if it was confined to participants able to give consent

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iii) Balance between benefit and risk, burden and intrusion
The research is of potential benefit to participants lacking capacity without imposing a
disproportionate burden. The REC noted that while the research may not benefit participants
directly, it is intended to provide knowledge of the causes, treatment or care of the condition
affecting participants lacking capacity. After discussing the REC agreed that the risk to
participants is negligible, the research will not significantly interfere with their freedom of action or
privacy, and it will not be unduly invasive or restrictive.

iv) Arrangements for appointing consultees
The REC considered the arrangements set out in the application for appointing consultees under
section 32 of the Mental Capacity Act to advise on whether participants lacking capacity should
take part and on what their wishes and feelings would be likely to be if they had capacity.
The Committee queried that method of identifying/appointing Consultees.
Dr Sinai clarified that an assessment of capacity will be conducted and the referral centres
(Community Learning Disability Team) will identify potential participants who are deemed to have
capacity. The research team will meet with them directly.
For potential participants who are deemed to lack capacity the LDT will be in a position to identify
a consultee (family members, next of kin, unpaid carer, etc) and the research team will make
arrangements to meet with them prior to approaching the participant. The LDT will also be in a
position to make arrangements to appoint a nominated Consultee if required. After discussion the
REC agreed that reasonable arrangemtns were in place for identifying personal consultees and
for appointing nominated consultees independent of the project where no persona can be
identified to act as a personal consultee.

v) Information for Consultees
the REC reviewed the information to be provided to consultess about the proposed research
hand their role and responsibilities as a consultee. The REC was satisfied that the information
was adequate to enable consultees to give informed advice about the participants of persons
lacking capacity.

vi) Additional safeguards
The REC was satisfied that reasonable arrangements would be in place to comply with the
additional safeguards set out in section 33 of the Mental Capacity Act.

vii) Other ethical issues
As the project involves adults lacking capacity the Committee is satisfied that the team have the
competencies required and an understanding of the relevant aspects of the MCA and code of
Practice, including the core principles of the Act, the assessment of capacity and the safeguards
relating to research.

The Committee is satisfied that the requirements of section 31 of the Act will be met in relation to
research carried out as part of this project on, or in relation to, a person who lacks capacity to
consent to taking part in the project – and approved this research project for the purposes of the
Mental Capacity Act 2005.

Adequacy and completeness of Participant Information

The Committee agreed that generally the procedures described in the protocol have been
addressed in the Information Sheet, but felt that some corrections are needed:

i) The Committee noted that the Participant Information Sheet lay title mentions dementia and
may cause undue worry for participants in the control group. You clarified that you are specifically
recruiting participants with dementia/Down syndrome but would be willing to amend the title in
view of the Committee's comments

ii) The Committee also noted that the Participant Information Sheet has no complaints section,
and contact details. You agreed to rectify.

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Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

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

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

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where 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 approvals from host organisations

Other conditions specified by the REC

The favourable opinion is subject to the following conditions being met prior to the start of the study: ·

In the Participant Information Sheet

i) The Committee requested that the team considers amending the lay title of the project to avoid mentioning 'dementia'
ii) The Committee requested that a complaints section is added to the Participant Information Sheet to detail how and to whom potential complaints regarding the conduct of the study could be addressed (this is generally the sponsor)

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Confirmation should also be provided to host organisations together with relevant documentation

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Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Covering Letter		28 November 2011
REC application (submission 94289/270880/1/560)		01 December 2011
Protocol	1.5	28 November 2011
Summary/Synopsis	1	28 November 2011
Advertisement: Recruitment Poster/Flyer	1.1	22 November 2011
Coer letter and letter of invitation to participant	1	21 November 2011
Participant Information Sheet: easy read	1.5	28 November 2011
Participant Information Sheet: Carer/Consultee	1.5	28 November 2011
Participant Information Sheet: the role of a Consultee	1.3	21 November 2011
Information sheet for professionals	1.5	28 November 2011
Other: Data Collection Form	1.4	23 November 2011
GP/Consultant Information Sheets: Learning Disability Team	1.1	28 November 2011
Participant Consent Form: easy read	1.5	28 November 2011
Participant Consent Form: Consultee	1.5	28 November 2011
Other: Thank you letter to participant	1.1	22 November 2011
Feed-back letter to GP/Learning Disability Team	1.1	24 November 2011
Investigator CV (Chief Investigator: Andre Strydom)		
Investigator CV (Academic supervisor: Angela Hassiotis)		
Investigator CV (Student: Amanda Sinai)		28 November 2011
Letter from Sponsor		15 November 2011
Letter from Statistician		24 November 2011
Evidence of insurance or indemnity		15 August 2011

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.
No conflicts of interest were declared in relation to this application

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

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

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The NRES 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 website.

Further information is available at National Research Ethics Service website > After Review

| 11/WA/0369 | Please quote this number on all correspondence |

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

Yours sincerely

Rossela Roberts

Mr David Owen
Chair

Email: rossela.roberts@wales.nhs.uk

Enclosures: List of names and professions of members who were present at the meeting
                and those who submitted written comments

                "After ethical review – guidance for researchers"

Copy to: Sponsor: Mr Rajinder Sidhu, University College London
            R&D Office: Mr Pushpsen Joshi, North Central London Research Consortium (NOCLOR)

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Participant information sheet

A study about how different parts of the brain work in older people with Down's syndrome

Insert picture of researcher	my name is Amanda Sinai
	I am doing some **research** Research is when we ask people questions and do tests to find out things
	I am writing to ask if you would like to help me
	To help you understand this letter you can • ask someone to read it for you
	• talk to your carer about it

What is my work about?
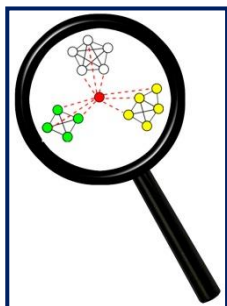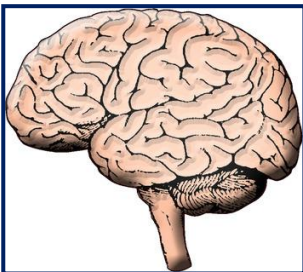
I am finding out about older people with Down's syndrome

- I want to find out how different parts of the brain work in older people with Down's syndrome

- I want to find out if this is different for people with Down's syndrome and dementia

- I want to find out if there are genetic reasons for this

Why do I want to see you?

I want to talk to you

- because you have Down's syndrome

- because you are 45 years old or older

- The information you give can help to make things better for people with Down's syndrome

What will happen if you take part?

If you agree to take part

- I will ask you and your carer some **questions**

- I will ask your **care team** some questions

- your carer will fill in some **forms**

- you will do some **tests** – these are like games

- some of the tests will be on a **computer**

- I will check your **blood pressure and general physical health**

- I will collect some of your **spit** (saliva)

  - I will give you a cup with a small sponge on a stick
  - I will ask you to put the sponge in your mouth
  - this is to soak up some of your spit (saliva)

  - Then we will put the sponge in the cup
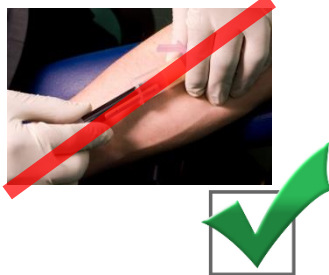
- I will ask you to have a **blood test**

  - the blood test may hurt a little

  - It is **OK** if you do not want the blood test

2 - 3 hours

the meeting will last for about **2 or 3 hours**

we can meet at a place you know like your **home**

your carer or worker will also come to the meeting

Do you have to take part?

	you can tell me **Yes** if you want to take part
	you can tell me **No** if you do not want to take part
	if you say no it will **not** change the care you get
	if you decide to take part, I will ask you to sign a **consent form**
	you can stop taking part at any time
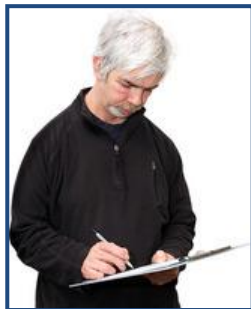
What happens after you have seen me?
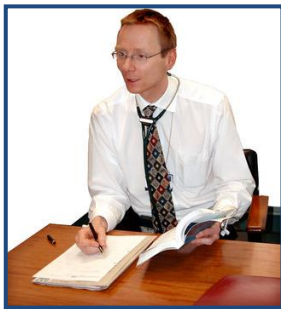
If you tell me it's **OK** I will

- ask your doctor or care team about you

- tell your doctor about the tests we did

- tell your care team about the tests we did

- send you a copy of your results

We will test your blood or spit in a laboratory

- we may keep it in the laboratory for more tests

- we may need to send it to another place so that they can look at it

- we will take out your name if we send it away

We will also put the test results on a computer

- other people can then look at the information
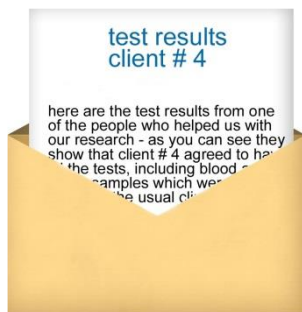
But they will not know it is about you – we will take out your name and where you live (**personal information**) before it goes on the computer

I will give you a **small gift or gift voucher** to say thank you

if you take part in my study

- the information you give will be confidential

- I will not talk to anyone else about you without asking you first

- I will not use any information with your name and address
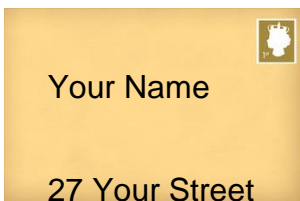
Your Name

27 Your Street

But I would like to keep your name and address on a list

This is so we can contact you if we need

- more information

	• to do more research

If you want to talk to me

	you can phone me or you can email me
	• if you would like to take part in the study
	• if you have any questions about the study
	• if you are unhappy about something

my phone number is

020 76 79 90 33

my email address is

a.sinai@ucl.ac.uk

If you are unhappy about something, you can also talk to your local PALS team

Their phone number is

(insert local phone number)

Thank you for looking at this

This research project has been reviewed by the North Wales - West Research Ethics Committee, who are there to make sure you are treated well.

Carer/Consultee Information sheet

A study about how different areas of the brain work in older people with Down's syndrome

My name is Amanda Sinai and I am a higher trainee in the Psychiatry of Learning Disability. I am carrying out research to examine the specific differences in cognitive functions (brain functions) between people with Down's syndrome who have dementia and those who do not have dementia. The study is funded by the Baily Thomas Charitable Fund and sponsored by University College London, where I will be working towards an MD (Res). The study has been reviewed by the North Wales - West Ethics Committee.

About the research project

What is the importance of the study?

People with Down's syndrome are known to have higher rates of dementia. People with Down's syndrome may also have changes in specific brain functions. For example, they might have specific problems with short term memory.

An assessment to measure these brain functions has been developed for adults with Down's syndrome. It is called the ACTB (Arizona Cognitive Test Battery). It has not been tested in older adults with Down's syndrome and dementia. This is important because it would increase our understanding of specific brain functions and dementia in people with Down's syndrome. It could later be used to improve assessment and management of people with Down's syndrome and dementia.

We plan to assess the ACTB in older adults with Down's syndrome, including whether it can detect differences between people who have dementia and those who do not.

We will ask participants to give a blood or saliva sample for genetic (DNA) analysis. This will be used to determine whether genetic factors might be related to changes in brain function in older people with Down's syndrome who develop dementia.

Who is eligible?

We are looking for people with Down's syndrome, aged 45 and above. We are recruiting people both with and without a diagnosis of dementia. Participants will need to be able to understand simple verbal commands and perform simple puzzles and games. We will include people who have stable and treated mental or physical health problems. We will not be able to include people who have untreated thyroid problems or epilepsy, or active psychosis or mood disorders. We will not be able to include people who have had a previous stroke or a significant head injury.

We will include people who lack capacity to consent to the study. If a participant lacks capacity, we have to seek an opinion from a personal or nominated consultee.

What will the assessment involve?

We will recruit participants with Down's syndrome with and without dementia.

Participants will take part in a 2 – 3 hour assessment which will involve them completing tests (like games) on a touchscreen computer tablet and using tabletop tools. Relatives or carers will be asked to present during the meeting and will be asked to complete informant questionnaires during this time. Participants will be given a break half way through the interview, or more as required.

We will collect some basic information about the participants from them and their carers. We may also discuss participants with their community learning disability team and look at their patient records.

We will check participants' blood pressure and general physical health. We will also take a blood test or a saliva sample for genetic (DNA) and related biomarker analysis.

The assessment will be arranged at a time and place that is convenient for the participants; this may include their home address or their local community learning disability team.

What happens after the assessment?

We will send a summarised report of our findings to the participant, their care team and their GP. We will also provide a small gift or gift voucher to all participants as a way of saying thank you.

Genetic analysis may be performed in laboratories outside University College London. Occasionally the analysis may have to be performed outside the UK in which case only fully anonymised samples will be released.

If a participant who has not been diagnosed with dementia by the care team has a score suggestive of dementia on the cognitive assessment, we will let the care team know, who can then take the appropriate action. We do not think that genetic tests will reveal any findings that are important to the health of the participant. However, we will seek consent from the participants to contact their learning disability teams and/or GPs if we find known genetic problems that are important to their health (apart from those related to Down syndrome) so that they can be considered for referral to a clinical geneticist for further input.

The results from the study, including the genetic results, will be stored on a database. These will be anonymised. The results may be sent to other researchers or shared with other researchers (these will be anonymised).

All personal data will be handled in accordance with the Data Protection Act. Personal data will be securely held on the UCL IT system. Access will be restricted to the study Chief and Principle Investigators and their nominated researchers. Personal data will be stored separately from the genetic and clinical database. Personal data will not be disclosed without the consent of the participant (or consultee if the participant does not have capacity to consent). However, if there are vulnerable adult concerns, a keyworker or social worker may need to be informed and if there are health concerns, the participant's care team or GP may need to be informed.

Biological samples will be anonymised at the point of collection. The Chief and Principle Investigators will be the guardians of the anonymisation codes which will be held securely.

Anonymised paper records will be stored securely within the Faculty of Brain Sciences at University College London. The anonymised genetic and clinical data will be entered into an electronic database held within the Faculty of Brain Sciences at University College London.

Anonymised samples may be shared with other research groups who are conducting research in the field of learning disabilities. Samples may be stored for use in future research.

Anonymised data may be shared with other research groups or entered onto publically accessible databases such as Decipher. This is standard practice

in genetic studies, and the best way to quickly share information about new genetic findings with other researchers and clinicians across the world.

We would like to keep a record of participant's contact details so that we can contact them if we need more information or if we are thinking about doing more research.

What are the risks and benefits of the study?

There are few risks to potential participants (except for possible frustration and anxiety when completing the tasks). Frustration and anxiety will be minimised by giving one planned break and having the option of further breaks if appropriate.

Saliva sample collection may be slightly uncomfortable, but should not hurt. Risks of blood tests are known, and include mild pain, some bleeding and bruising. We can use a cream before the blood test to reduce pain. If it is more convenient, we can arrange for the blood test to be taken at the same time that the participant is due to have routine blood tests.

This study will benefit participants as it will provide baseline tests, against which future change can be measured. By increasing knowledge about people with Down's syndrome and people with dementia, it may also benefit others in the future.

A decision to withdraw at any time, or a decision not to take part, will not affect any aspects of care.

Advice and complaints

If you have any concern about any aspect of this study, you or someone you trust should ask to speak to Amanda Sinai or a member of your care team who will do their best to answer your questions. If you remain unhappy, you can contact your local PALS (Patient Advice and Liaison Service) team (insert local telephone number) or you can complain formally through the NHS Complaints Procedure (details can be obtained from your local PALS team).

Please feel free to contact me if you have any questions.

Thank you for taking the time to read this letter

Details of contact person

My name: Amanda Sinai

Address: Department of Mental Health Sciences,

University College London,

2nd Floor Charles Bell House,

67-73 Riding House Street,

London

W1W 7EY

E-mail address: a.sinai@ucl.ac.uk

Telephone: 020 76 79 90 33

Consent form - participant

Participant Identification Number:
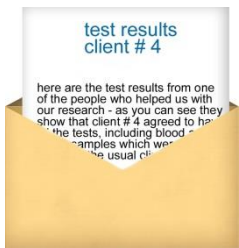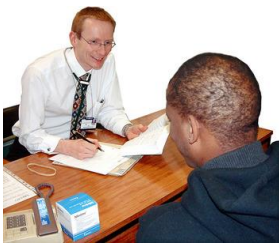
A study about how different parts of the brain work in older people with Down's syndrome

Please tick **no** ✗ or **yes** ✓ for each part	✗	✓
I have read the information sheet about the research		
I can understand the information sheet		
I could ask questions if I wanted to		

Please tick **no** ❌ or **yes** ✔ for each part	❌	✔
I understand that it is my choice to take part in this study		
I understand that I can say **no** at any time if I want to stop		
I understand that it will not change the care I get		
you can ask my doctor or care team about me you can look at my doctor's notes		

Please tick **no** ✗ or **yes** ✓ for each part	✗	✓
I agree to take part in this study		
you can check my **blood pressure and general health**		
I agree that you can put the **sponge in my mouth**		
I agree to have a **blood test**		

Please tick **no** ❌ or **yes** ✔ for each part	❌	✔
you can send my blood or spit to other researchers – they will not know my name		
you can store my test results on a computer		
you can share my test results with other researchers – they will not know my name		
you can share my test results with my doctor		
you can share my test results with my care team		

Please tick **no** ❌ or **yes** ✔ for each part	❌	✔
you can keep my blood or spit in the laboratory for more tests		
I want to know my test results		
you can get in touch with me again if you need to		

	my name	my signature
	date	
	researcher's name	their signature
	date	

- 1 copy will be given to the participant
- 1 copy will be kept by the researcher
- 1 copy will be stored in the medical file

Consultee Consent form

Participant Identification Number:

A study about how different areas of the brain work in older people with Down's syndrome

As someone who knows _____ (person's name) well/in an independent capacity, you are being invited to consider whether _____ (person's name) who lacks capacity, would want to participate in the research study based on your knowledge of him/her.

We ask you to be a consultee because _____ (person's name) is unable to understand the information provided in the information leaflet or is unable to make independent decisions and communicate them.

It is up to you to decide whether or not they would want to take part based on your knowledge of the person and the information you have been given. Be reassured that even if you decide that they can take part, he/she is still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect any aspects of care.

	Please initial if you agree
I have read the information sheet about the research. I have had chance to ask questions and talk about this study. I have got enough information about this study.	
I confirm that I have agreed to act as a consultee for the above named person. I understand that my role as consultee is to advise the research team as to the above named persons' likely wishes and feelings in relation to entering the study.	
I understand that the participant can stop taking part in this study at any time and does not have to give a reason. I understand that participation in the study will	

not change the help that the participant receives.	

Are you aware of any advance directives that may be relevant to participation in this research? If yes, please detail further:	Yes/No

	Please initial if you agree
It is appropriate for _____ to participate in this study	
It is appropriate for_____ to have their blood pressure and general health checked	
It is appropriate for_____ to give a sample of saliva for genetic analysis	
It is appropriate for_____ to have a blood test for genetic and biomarker analysis	
I agree that their blood, saliva or DNA can be sent to other researchers (this will be anonymised)	
I agree that their samples can be stored for use in future research	
I agree that their test results can be stored on a database	
I agree that their test results can be shared with other researchers, including publically accessible databases (this will be anonymised)	
It is appropriate for the researcher to discuss_____ with their care team and send them a summary of the findings	
It is appropriate for the researcher to send their GP a	

summary of the findings	
It is appropriate for the researcher to send_____ a summary of the findings	
It is appropriate for the researcher to get in touch with the participant again if they need to	

Any further comments or preferences from the consultee:

Signed: Name in Block Letters:

Date: Relation to participant:

Researcher' signature: Name in Block Letters:

Date:

- 1 copy will be given to the participant
- 1 copy will be given to the consultee
- 1 copy will be kept by the researcher
- 1 copy will be stored in the medical file

Data Collection form

Assessing specific cognitive deficits associated with dementia in older adults with Down's syndrome: a London based study

Participant name	
Participant address	
Participant telephone number	
Informant name	
Relationship to participant	
Consultee name	
Consultee address	
Consultee telephone number	
Participant GP name	
Participant GP address	
Participant identification number	

Participant Identification Number	
Date of assessment	
Referral centre	
Gender	
Age	
Level of learning disability	
Type of Accommodation (independent living, supported accommodation etc.)	
Ethnic origin	
Capacity to consent to study	
Capacity to consent to DNA sample	
Relationship of informant to participant	
Frequency of contact between informant and participant	
Premorbid IQ level	
Genetic diagnosis Down's syndrome	
Family history Down's syndrome	
Family history dementia	
Diagnosis of dementia	
Type of dementia	
Date of diagnosis	

Physical Examination:	
• Blood Pressure	
• Pulse	
• Height	
• Weight	
• Abdominal circumference	
• Neurological findings:	
Medical problems:	
• Thyroid problems	
• Epilepsy	
• Date epilepsy started	
• History of stroke	
• History of head injury	
• Falls	
• Congenital cardiovascular problems	
• Diabetes	
• Smoker	
• Other	
Sensory problems:	
• Hearing	
• Date hearing problems started	
• Visual problems	
• Date visual problems started	
• Using any corrective methods	
Psychiatric history:	
• Psychosis (active or treated)	

• Bipolar disorder	
• Depression	
• Date of last episode	
• How many episodes	
• Other	
Medication:	
Supplements (eg. Vitamins)	
Recent investigations:	
• Full Blood count	
• Thyroid tests	
• B12 levels	
• ECG	
• EEG	
• Head scan	
• Other	

Any other relevant information:

Table A1 – Skewness and Kurtosis of the cognitive tests

	Dementia		No Dementia	
	Skewness	Kurtosis	Skewness	Kurtosis
K-BIT II - Total raw score	2.817	9.101	0.731	-1.058
K-BIT II - Verbal subscale	2.828	9.789	0.884	-0.538
K-BIT II - Non verbal subscale	2.073	3.978	0.575	-1.401
CANTAB tests:				
CANTAB PAL first trial memory score	1.404	2.097	1.677	2.744
CANTAB PAL stages completed	0.463	0.545	0.791	-0.579
CANTAB IED – Stages completed	0.941	-0.785	0.913	-0.971
IED – Errors block 1	-0.230	-1.362	0.042	-1.805
Modified dots task – 2nd stage	-0.903	1.606	0.664	-1.068
Modified dots task – 3rd stage	-0.397	-1.081	0.498	1.724
CANTAB SRT	-0.151	-1.448	0.500	-0.836
Finger sequencing task	1.272	1.819	1.193	0.377
NEPSY visuomotor precision – Train and Car	-0.332	-1.445	-1.44	-1.264
NEPSY visuomotor precision – Car and Motorbike	1.563	3.759	0.939	-0.457
Table top tests:				
Verbal Fluency Raw score	0.797	0.396	0.643	0.496
Verbal Fluency Adjusted	0.113	-0.856	-0.017	0.627
Tower of London - Stages succeeded on	-0.160	-1.694	0.146	-0.893
Tower of London - Points	0.094	-1.444	0.496	-0.990
Object Memory	0.361	-0.656	-0.488	-0.156
Memory for sentences	0.081	-0.885	0.984	-0.013
Finger-nose	0.514	-0.566	0.868	0.253
Gait	0.079	-0.126	0.571	-0.624

Table A2 – Floor and ceiling levels of K-BIT II according to level of intellectual disability

	Level of ID	Dementia		No Dementia	
		Number at floor (%)	Number at ceiling (%)	Number at floor (%)	Number at ceiling (%)
K-BIT II total raw score	Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Moderate/ Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
K-BIT II verbal subscale	Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Moderate/ Severe	1 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
K-BIT II non verbal subscale	Mild	1 (20.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)
	Moderate/ Severe	3 (33.3%)	0 (0.0%)	2 (15.4%)	0 (0.0%)

Table A3 – Floor and ceiling levels of ACTB tests according to level of intellectual disability

	Level of ID	Dementia		No Dementia	
		Number at floor (%)	Number at ceiling (%)	Number at floor (%)	Number at ceiling (%)
CANTAB PAL first trial memory score	Mild	2 (66.7%)	0 (0.0%)	1 (12.5%)	0 (0.0%)
	Moderate/ Severe	3 (42.9%)	0 (0.0%)	5 (41.7%)	0 (0.0%)
CANTAB PAL stages completed	Mild	2 (66.7%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
	Moderate/ Severe	1 (14.3%)	0 (0.0%)	1 (8.3%)	0 (0.0%)
CANTAB IED stages completed	Mild	2 (50.0%)	0 (0.0%)	2 (25.0%)	0 (0.0%)
	Moderate/ Severe	4 (66.7%)	0 (0.0%)	5 (41.7%)	0 (0.0%)
CANTAB IED errors block 1	Mild	n/a	1 (25.0%)	n/a	2 (25.0%)
	Moderate/ Severe	n/a	0 (0.0%)	n/a	1 (8.3%)
Modified dots task 2nd stage	Mild	2 (66.7%)	0 (0.0%)	3 (37.5%)	3 (37.5%)
	Moderate/ Severe	4 (100%)	0 (0.0%)	7 (87.5%)	0 (0.0%)
Modified dots task 3rd stage	Mild	2 (66.7%)	0 (0.0%)	4 (50.0%)	0 (0.0%)
	Moderate/ Severe	4 (100%)	0 (0.0%)	7 (87.5%)	0 (0.0%)

	Level of ID	Dementia		No Dementia	
		Number at floor (%)	Number at ceiling (%)	Number at floor (%)	Number at ceiling (%)
CANTAB SRT median latency	Mild	n/a	n/a	n/a	n/a
	Moderate/ Severe	n/a	n/a	n/a	n/a
Finger sequencing task	Mild	1 (33.3%)	0 (0.0%)	0 (0.0%)	2 (28.6%)
	Moderate/ Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%)
NEPSY visuomotor precision train and car	Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Moderate/ Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
NEPSY visuomotor precision car and motorbike	Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Moderate/ Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table A3 continued – Floor and ceiling levels of ACTB tests according to level of intellectual disability

Table A4 – Floor and ceiling levels of table top tests according to level of intellectual disability

	Level of ID	Dementia		No Dementia	
		Number at floor (%)	Number at ceiling (%)	Number at floor (%)	Number at ceiling (%)
Verbal fluency raw score	Mild	1 (33.3%)	n/a	0 (0.0%)	n/a
	Moderate/ Severe	2 (33.3%)	n/a	1 (8.3%)	n/a
Verbal fluency adjusted	Mild	1 (33.3%)	n/a	0 (0.0%)	n/a
	Moderate/ Severe	2 (33.3%)	n/a	1 (8.3%)	n/a
Tower of London stages completed	Mild	3 (75.0%)	0 (0.0%)	0 (0.0%)	5 (71.4%)
	Moderate/ Severe	2 (28.6%)	0 (0.0%)	1 (9.1%)	0 (0.0%)
Tower of London points	Mild	3 (75.0%)	0 (0.0%)	1 (14.3%)	2 (7.4%)
	Moderate/ Severe	3 (42.9%)	0 (0.0%)	4 (36.4%)	0 (0.0%)
Object memory	Mild	2 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Moderate/ Severe	4 (57.1%)	0 (0.0%)	0 (0.0%)	2 (18.2%)
Memory for sentences	Mild	1 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Moderate/ Severe	1 (14.3%)	0 (0.0%)	1 (8.3%)	0 (0.0%)
Finger-nose	Mild	0 (0.0%)	n/a	0 (0.0%)	n/a
	Moderate/ Severe	0 (0.0%)	n/a	0 (0.0%)	n/a
Gait assessment	Mild	1 (33.3%)	n/a	0 (0.0%)	n/a
	Moderate/ Severe	1 (14.3%)	n/a	0 (0.0%)	n/a

Publications and presentations related to this study

Publications

Sinai A, Chan T, Strydom A (2014). Epidemiology of dementia in people with intellectual disability. In: Intellectual Disability and Dementia Research into Practice. Ed: Watchman K, Jessica Kingsley Publishers.

Strydom A, Sinai A. (2014) Dementia. In: Handbook of Psychopathology in Intellectual Disability: research practice and policy. Eds: Tsakanikos E, McCarthy J, 191-204. Springer.

Sinai A, Bohnen I, Strydom A. (2012) Older adults with intellectual disability. Current Opinion in Psychiatry, 25, 359-364.

Presentations

This study has been presented to several audiences, including:

Pan-London Learning Disability Consultants meeting, The Kingswood Centre, 2012

Down's Syndrome Research Group, University of Arizona, 2012

Margaret Slack Presentation, Royal College of Psychiatrists International Congress, Edinburgh, 2013

Centre for Ageing and Mental Health Science Meeting, University College London, 2013