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# An MRI and H1-MRS study of dementia in down's syndrome and alzheimer's disease in the general population.

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# Candidate thesis declaration

I declare that this thesis, which I submitted to RCSI for examination in consideration of the award of a higher degree of Doctor of Medicine (MD), is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme, this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in RCSI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that the work is original, and, to the best of my knowledge, does not breach copyright law, and has not been taken from other sources except where such work has been cited and acknowledged within the text.

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# Abstract


## Introduction

Dementia is a progressive and largely irreversible clinical syndrome which is characterised by a disturbance of higher cortical functioning, occurring in clear consciousness. Alzheimer's disease is the most common form of dementia. People with Down's syndrome, the most common genetic cause for intellectual disability, have a significantly increased risk for developing Alzheimer's disease in later life.

Neuroimaging is an important tool in the preclinical detection and monitoring of Alzheimer's disease. Much attention has focused on volumetric manual Region of Interest MRI studies to investigate changes confined to a limited set of brain regions. Automatic techniques have been developed to study more widespread brain volume and thickness measures than Region of Interest MRI studies. Proton Magnetic Resonance Spectroscopy (H1-MRS) can be employed to investigate the concentrations of a number of brain metabolites including N-acetylaspartate [NAA], myo-inositol [mI], choline [cho] and creatine plus phosphocreatine [Cr+PCr]. NAA is hypothesized to be a marker of the number of viable neurons. Elevation of mI is a marker for gliosis.

To my knowledge, no in vivo case-control study exists comparing the anatomy of dementia in Down's syndrome to people with Alzheimer's disease in the general population.

## Methodology

Subjects were scanned using a 1.5 Tesla, GE NU/i Signa MR System at the Maudsley Hospital in London. The reformatted SPGR data set was analysed using Measure Software. Volumetric analysis of the hippocampi, temporal lobes, lateral ventricles, whole brain and total cranial volumes were performed by means of manually tracing regions of interest to compare subjects with Down's syndrome to those with Alzheimer's disease in the general population. In addition, an automated technique enabled the investigation of more widespread brain volume and thickness measures in subjects with Down's syndrome, Alzheimer's disease and age-matched healthy controls. Additional volumetric analysis was undertaken on MRI scans of subjects with Alzheimer's disease, mild cognitive impairment and Alzheimer's disease healthy controls at baseline and on subjects who were re-scanned after 12 months. Magnetic resonance spectroscopy was used to investigate differences in hippocampal metabolite concentrations between subjects with Down's syndrome, Alzheimer's disease and age-matched healthy controls.

## Results

Subjects with dementia had a significant reduction in the volume of the hippocampus, temporal lobe and whole brain and an increase in the volume of the lateral ventricles, compared to their non-demented controls. There was a significant correlation between atrophy of the hippocampus and temporal lobe, and cognitive decline. Significant differences were demonstrated for more global cortical volume and thickness

measures between demented and non-demented subjects, and between subjects with Alzheimer's disease and demented subjects with Down's syndrome.

In the longitudinal study, when compared to age matched healthy controls, subjects with Alzheimer's disease had a significant reduction in the volume of the hippocampus and temporal lobe, and an increase in the volume of the lateral ventricles at baseline and when re-scanned at 12 months, and subjects with mild cognitive impairment had findings intermediate between those of Alzheimer's disease and age matched healthy controls.

The Alzheimer's disease group had a significant reduction in [NAA] compared to its age matched healthy control group but not when compared to demented subjects with Down's syndrome or younger Down's syndrome healthy control groups. Demented subjects with Down's syndrome had a significantly higher [mI] than the other groups.

## Conclusion

MRI and H1-MRS are useful tools to compare the anatomy of dementia in Down's syndrome to subjects with Alzheimer's disease in the general population. Significant differences between demented and non-demented subjects can enable the distinction between subjects with and without dementia, and may distinguish between individuals with Alzheimer's disease and demented subjects with Down's syndrome.

# Chapter 1

# Introduction

## 1.1 Dementia

### 1.1.1 General introduction

Dementia is a progressive and largely irreversible clinical syndrome which is characterised by a disturbance of higher cortical functioning, occurring in clear consciousness. Dementia incorporates a variety of symptoms which include a decline in memory, reasoning and communication abilities, and a gradual loss of skills needed to carry out activities of daily living.

Between 25-75% of elderly people report that their memory is worse compared to when they were younger, depending on how the question is phrased (Jonker *et al.*, 2000; Hanninen *et al.*, 2002). Although the majority of elderly people who note memory changes will not go on to develop dementia, the prevalence of dementia in people over the age of 65 years is 5%, and is 20% in individuals over 80 years. Dementia should not be considered to be a feature of normal aging.

Worldwide, the annual economic cost of dementia has been estimated as US$315 billion. The total annual costs per person with dementia have been estimated as US$1,521 in a low income country, rising to US$4,588 in middle income countries, and US$17,964 in high income countries (Alzheimer's Disease International, 2009). Research from North America and recent findings from the 10/66 Dementia Research Group's population-based studies in Latin America, India and China; indicate consistently that dementia is the leading cause of dependency and disability among older people (Alzheimer's Disease International, 2009).

Dementia reduces the lifespan of affected individuals. In the developed West, a person with dementia can expect to live for approximately 5-7 years after the onset/diagnosis of the condition (Ganguli *et al.,* 2005; Fitzpatrick *et al.,* 2005). In low and middle income countries, diagnosis is often delayed, and survival may be considerably shorter (Kalaria *et al.,* 2008). Dementia has already been established as one of the major challenges of this century (Berr *et al.,* 2005). According to the Global Burden of Disease estimates for the 2003 World Health Report (WHO, 2003), dementia contributed to 11.2% of years lived with a disability in people aged 60 years and older, more than stroke (9.5%), musculoskeletal disorders (8.9%), cardiovascular disease (5%) and all forms of cancer (2.4%).

It was estimated that there were 35.6 million people worldwide living with dementia in year 2010 (Alzheimer's Disease International, 2009). It has been predicted that the number of people living with dementia will nearly double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050 (Alzheimer's Disease International, 2009). More than half (58%) of all people with dementia worldwide live in low and middle

income countries, which is expected to rise to 71% by 2050 (Alzheimer's Disease International, 2009). The number of people worldwide living with dementia is an important indicator of the impact of the disease.

In 2000, prevalence data from 11 European population based studies were pooled to obtain stable estimates of the prevalence of dementia in people over the age of 65 years (Lobo *et al.,* 2000). The prevalence figure for all causes of dementia was 6%, with 4.4% being attributed to Alzheimer's disease and 1.6% to vascular dementia. Alzheimer's disease is the most common neurodegenerative disorder among the elderly and is the commonest cause of dementia. It has been estimated that 26% of women and 21% of men over the age of 85 years have some form of dementia, of which approximately 50% have Alzheimer's disease (Melzer *et al.,* 1997). Early surveys from South East and East Asian countries provide an exception, with an equal distribution of Alzheimer's disease and vascular dementia (The 10/66 Dementia Research Group, 2000). More recent research suggested this situation has now reversed (Prince *et al.,* 2008; Department of Health, 2009).

Alzheimer's disease is characterised by a progressive cognitive decline and cerebral atrophy. The neuropathology changes associated with Alzheimer's disease commences in the entorhinal cortex before spreading to the hippocampus and eventually to the cortex (Braak & Braak, 1991). The studies of Braak & Braak (1991; 1995; 1999) in conjunction with others (Hyman *et al.,* 1986; Mann *et al.,* 1988; Arriagada *et al.,* 1992a; 1992b; Berg *et al.,* 1993; Masliah e*t al.,* 1994; Masliah, 1995) suggest that neurodegeneration of the transentorhinal region results in the disruption of the perforant pathway circuitry in the very early stages of Alzheimer's disease. As

Alzheimer's disease advances, the rate of cognitive decline increases (Morris *et al.,* 1993; Galasko *et al.,* 2000). The brain changes underlying Alzheimer's disease probably develop over a period of at least 20-30 years before symptoms become noticeable (Alzheimer's Disease International, 2009).

Neuronal dysfunction and death occurs in multiple regions of the central nervous system in people with Alzheimer's disease. This results in alterations in synaptic inputs, predominantly in the amygdala, hippocampus and neocortex (Whitehouse *et al.,* 1982; Hyman *et al.,* 1984; Terry *et al.,* 1991). Neurofibrillary tangles are contained in the cell bodies and proximal dendrites of the vulnerable neurons in Alzheimer's disease. Furthermore, the brains of people with Alzheimer's disease show extracellular deposits of β amyloid. Neurons in the transentorhinal/entorhinal region produce very high levels of β amyloid precursor protein compared to other neuronal groups (Roberts *et al.,* 1993; Masliah, 1995).

Several biochemical mechanisms may contribute to neuronal degeneration, with the final pathways involving both the cleavage of β amyloid precursor protein to form β amyloid (a major component of senile plaques), and abnormal processing and accumulation of tau protein (a major component of neurofibrillary tangles) (Blessed *et al.,* 1968; Selkoe, 1999; St George-Hyslop *et al.,* 2000). Changes in the configuration and phosphorylation of tau are early events in neurofibrillary lesions and result in a loss of the microtubule-binding properties of tau (Spillantini & Goedert, 1998).

Plaques in the cerebral grey matter were first described by Blocq & Marinesco (1892) and were related to the pathology of senile dementia by Simchowicz (1910) who

coined the term 'senile plaque'. Neurofibrillary change was described in 1907 (Alzheimer, 1907). Alzheimer's disease was named after the German neurologist Alois Alzheimer (1864–1915), who was the first to describe the condition. In 1906, he studied a 51 year old lady known as Auguste D, who was admitted to the state asylum in Frankfurt. Auguste D had a history of progressive difficulties with memory, language and behaviour. After the patient died, Alzheimer identified changes in brain pathology in an illness that bears Alzheimer's name.

The diagnostic hallmarks of the disease (i.e. neurofibrillary tangles and amyloid plaques) can only be established post mortem with histological examination of brain tissue. Studies have shown a correlation between cerebral grey matter plaque load and the severity of dementia (Blessed *et al.,* 1968; Caramelli *et al.,* 1998). Blessed *et al.* (1968) suggested that differences between well-preserved, mildly impaired, and unequivocally demented subjects were, as far as could be determined, of a quantitative nature. Blessed *et al.* (1968) concluded that the differences between grossly demented, mildly demented and well-preserved elderly individuals, might be due to a different rate of progression of plaque counts.

Naslund *et al.* (2000) undertook a post-mortem cross-sectional study of 79 nursing home residents in order to compare the levels of β amyloid variants in the cortices of subjects with no, questionable, moderate, or severe dementia. β amyloid variant levels were found to increase very early in the disease process. The results from Naslund *et al.* (2000) also indicated that increases in β amyloid variants preceded significant tau pathology at least in the frontal cortex, an area chosen for examination because of the absence of neuritic changes in the absence of Alzheimer's disease.

Van Hoesen *et al.* (1995) stated that certain cytoarchitectural fields (for example the entorhinal cortex) were particularly vulnerable for neurofibrillary tangle formation, while others (occipito/temporal area) were more vulnerable for plaque formation. Hyman (1984) found large numbers of neurofibrillary tangles in the subiculum and hippocampal CA1 field. Braak & Braak (1991) also found involvement in the neurons of layer II and IV of the entorhinal cortex.

Van Hoesen *et al.* (1995) suggested that the common denominator for the development of Alzheimer's disease was a multiple lesion effect rather than the quantity in any one cortical area. Van Hoesen (1995) proposed a neural system threshold model in which lesions accumulating in multiple loci disrupt feedback projections among association cortices and eventually result in cognitive impairment. This is in contrast with Braak & Braak (1991) who favoured a spread from the medial temporal lobe to other brain areas which did not correspond with hierachical vulnerability.

Choline acetyltransferase and acetylcholinesterase are enzymes that synthesise and degrade acetylcholine, both of which are significantly reduced in Alzheimer's disease compared to healthy controls. Choline acetyltransferase levels are reduced from 58-90% in the brains of subjects with Alzheimer's disease (Davies, 1978; Hansen *et al.*, 1988). Reduction of choline acetyltransferase, particularly in the temporal lobes, correlates with the severity of the dementia syndrome (Wilcock *et al.*, 1982). The reduction in choline acetyltransferase tends to parallel the distribution of histopathological abnormalities.

### 1.1.2 Aetiology and pathogenesis

The specific cause for Alzheimer's disease is unknown. Age and family history of the condition in first degree relatives are the strongest epidemiological risk factors for Alzheimer's disease. Below the age of 60 years, dementia is rare and is often associated with genetics and a strong family history of dementia. For late-onset Alzheimer's disease, both environmental (lifestyle) and genetic factors are important.

After advanced age, the most significant risk factor for late-onset Alzheimer's disease is a family history of Alzheimer's disease (Farrer *et al.*, 1997). Healthy individuals with a first-degree relative affected by Alzheimer's disease, especially a parent, are at a 4-10-fold higher risk for developing Alzheimer's disease as compared with individuals with a negative family history (Green *et al.,* 2002; Cupples *et al.,* 2004; Silverman *et al.,* 2005). Other risk factors for developing the condition include head trauma, education level, number of siblings, non-suburban residence, maternal age at birth, hypothyroidism and apolipoprotein E4 genotype (Van Dujin & Hofman, 1992; Morceri *et al.,* 2000).

The early-life environment and its effect on growth and maturation in children and adolescents are linked to many adult chronic conditions such as heart disease, stroke, hypertension, diabetes mellitus and chronic obstructive lung disease (Joseph, 1996) and to female reproductive outcomes. Alzheimer's disease may also have an early-life link (Emanuel, 1997). An association between early-life growth and development and later-life cognitive decline was first suggested by Conel (1939). Moceri *et al.* (2000) found that for each additional child in the family, the risk of Alzheimer's

disease increased by 8%. Growing up in a family with five or more siblings increases the risk of developing AD by 39%. The area of residence prior to age 18 years was found by Moceri *et al.* (2000) to be associated with Alzheimer's disease. Significantly more controls compared with case subjects grew up in the suburbs.

Studies which examined maternal age in Alzheimer's disease subjects have shown inconsistent results. Moceri *et al.* (2000) found no association between the mother's age at the patient's birth and subsequent onset of Alzheimer's disease. Farrer *et al.* (1991) found that advanced maternal age had a negligible effect on the risk of developing Alzheimer's disease. In contrast, maternal age of 40 years and over was found to be suggestively associated with a higher risk of Alzheimer's disease in the European Community Concerted Action in the Epidemiology and Prevention of Dementia (EURODEM) study (Rocca *et al.,* 1991). In subgroup analyses, the association was statistically significant for women and for sporadic cases.

Decreased paternal age has been associated with an increased susceptibility to Alzheimer's disease occurring after the age of 67 years (Farrer *et al.,* 1991). The higher incidence of late-onset Alzheimer's disease among people born to younger fathers is consistent with a genetic imprinting mechanism involving DNA methylation (Farrer *et al.,* 1991).

In the Framingham cohort, low cognitive performances measured more than ten years before the onset of dementia were found to be predictors of dementia (Elias *et al.,* 2000). Furthermore, measures of linguistic skills assessed 50 years prior to the

diagnosis of dementia have been found to be a future risk factor of developing Alzheimer's disease according to the Nun's study (Snowdon *et al.,* 1996).

A study of 321 cases of Alzheimer's disease undertaken by Scarmeas *et al.* (2006) found a steeper rate of decline over time in a composite measure of cognitive performance among those with more education. These findings were in agreement with previous studies (Teri *et al.,* 1995; Rasmusson *et al.,* 1996; Wilson *et al.,* 2004). Fritsch *et al.* (2002) investigated cognitive performance in 482 people with possible or probable Alzheimer's disease. A significantly slower rate of cognitive decline was detected among individuals with more education.

A total of 130 older Catholic clergy participating in the Religious Orders Study underwent annual cognitive function testing and brain autopsy at the time of death (Bennett *et al.,* 2003). The number of years spent in formal education and the global Alzheimer's disease pathology score were related to the level of cognitive function. The finding of the Religious Orders Study suggested that education not only provided a cognitive advantage such that people with more years of education had higher levels of cognitive function throughout adult life and therefore required more pathology to reach any given level of cognitive impairment, but that education somehow modified the effect of Alzheimer's disease pathology on cognition.

Koepsell *et al.* (2008) studied 2,051 participants over the age of 65 years. Higher education was found to be associated with higher MMSE scores when Alzheimer's disease neuropathology was absent or mild. With more advanced neuropathology, Koepsell *et al.* (2008) found that differences in MMSE scores among education levels

were attenuated. There was therefore no evidence detected of larger education-related differences in cognitive function when Alzheimer's disease neuropathology was more advanced.

Apolipoprotein E (apoE) has critical functions in redistributing lipids among central nervous system cells for normal lipid homeostasis, repairing injured neurons, maintaining synapto-dendritic connections and scavenging toxins (Mahley *et al.,* 2006). Through interactions with the Aβ peptide, apoE may increase Aβ deposition in plaques and impair its clearance (Mahley *et al.,* 2006). Non-neuronal cells, mainly astrocytes and to some extent microglia, are the major cell types that express apoE in the brain (Pitas *et al.,* 1987; Grehan *et al.,* 2001). In response to central nervous system stress or injury, neurons can synthesize apoE. ApoE4 undergoes neuron-specific proteolysis, resulting in bioactive toxic fragments that enter the cytosol, alter the cytoskeleton, disrupt mitochondrial energy balance and cause cell death (Mahley *et al.,* 2006).

ApoE ε4 allele is increased among people with late onset Alzheimer's disease (Najlerahim *et al.,* 1988; Burns *et al.,* 1989; Eberling *et al.,* 1992; Liu *et al.,* 1992; O'Brien *et al.,* 1992; Small *et al.,* 1995). In late onset families, the risk of Alzheimer's disease is increased from 20-90% with increasing number of ApoE ε4 alleles (Reiman *et al.,* 1996).

The neuropathological effects of human apoE4 with or without the involvement of Aβ have been clearly demonstrated in mice. Neuron-specific enolase promotor-apo E4 mice have shown significant learning impairment in a water maze and in vertical

exploratory behaviour (Raber *et al.*, 1998; 2000). Working memory was also impaired in transgenic mice expressing apoE in astrocytes (Fagan *et al.*, 2000).

### 1.1.3 Mild cognitive impairment

Mild cognitive impairment represents a stage of cognitive impairment that exceeds the normal expected age-related changes. Functional activities are largely preserved, and therefore mild cognitive impairment does not meet the criteria for dementia (Petersen, 2003). A person with mild cognitive impairment experiences memory problems greater than normally expected with aging, but does not show other symptoms of dementia such as impaired judgement or reasoning. One common classification distinguishes between amnestic and non-amnestic forms of mild cognitive impairment.

Studies using the criteria of Petersen (WHO, 2003; Ferri *et al.*, 2005), report an incidence rate of 10 per 1,000 person-years for mild cognitive impairment among elderly people without dementia (Larrieu *et al.*, 2002) and an annual conversion rate of 10-12% to Alzheimer's disease in subjects with mild cognitive impairment, in contrast to a conversion rate of 1-2% in healthy controls (Petersen *et al.*, 1999). Roundtree *et al.* (2007) reported that the conversion rate from amnestic mild cognitive impairment to Alzheimer disease was 56%, for amnestic sub-threshold mild cognitive impairment was 50%, and for non-amnestic mild cognitive impairment was 52%. For all mild cognitive impairment subtypes, the 4-year conversion to dementia was reported to be 56% (14% annually) and to Alzheimer disease was 46% (11%

annually) (Rountree *et al.,* 2007). Boyle *et al.* (2006) reported that individuals with mild cognitive impairment were almost 7 times more likely to develop Alzheimer disease compared with older individuals without cognitive impairment.

Amnestic mild cognitive impairment represents a transitional stage between normal aging and dementia (Morris, 2001). Alzheimer's disease is the main form of dementia in subjects with amnestic mild cognitive impairment who convert to dementia (Geslani *et al.,* 2005). Some researchers have found an association between smaller hippocampi and the observed annual conversion rate from mild cognitive impairment to Alzheimer's disease (WHO, 2003; Jack *et al.,* 2004), whereas others have not (Convit *et al.,* 2000; DeToledo-Morrell *et al.,* 2000; Dickerson *et al.,* 2001; Killiany *et al.,* 2002).

Early recognition of individuals with mild cognitive impairment will become increasingly important as treatments are developed that delay the transition from mild cognitive impairment to Alzheimer's disease. Delaying the onset of Alzheimer's disease by as little as 6 months should have substantial economic benefits (Brookmeyer *et al.,* 1998).

### 1.1.4 Diagnosis

Alzheimer's disease is characterised by a gradual onset, continued decline of memory and at least one additional cognitive domain that is not explained by another systemic or neurological disorder (McKhann *et al.,* 1984). The first symptoms usually include

deficits in recent or short-term memory. Subsequently, other cognitive domains such as language, orientation, judgement and long-term memory are affected. Behavioural problems such as social withdrawal, agitation and delusions gradually become increasingly more problematic, resulting in a significant proportion of patients ultimately requiring total care. The disease eventually contributes to death (Fradinger & Bitan, 2005).

A working Group on the Diagnosis of Alzheimer's Disease was established by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA). The Group established clinical criteria for the diagnosis of Alzheimer's disease of particular importance for research protocols (McKhann *et al.,* 1984). The most widely used clinical criteria for the diagnosis of Alzheimer's disase are the National Institute of Neurological and Communicative Disorders and Stroke Alzheimer's Disease and Related Disorder Association (NINDS-ADRDA) Criteria (McKhann *et al.,* 1984). The NINDS-ADRDA Criteria for the diagnosis of probable, possible and definite Alzheimer's disease are outlined in Table 1.1.

**(I). Criteria for the clinical diagnosis of Probable AD include:**

**a.** Dementia established by clinical examination and documented by MMSE or Blessed Dementia scale, confirmed by further neuropsychological tests

**b.** Deficits in two or more areas of cognition

**c.** Progressive worsening of memory and other cognitive functions

**d.** No disturbance of consciousness

**e.** Onset between the ages of 40 and 90 years, most often after age 65 years

**f.** Absence of systemic diseases or other brain diseases that could explain the cognitive changes.

**(II). The diagnosis of Probable AD is supported by:**

**a.** Progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia) and perception (agnosia)

**b.** Impaired activities of daily living and altered patterns of behaviour

**c.** Positive family history, particularly if documented neuropathologically

**d.** Lab results: Normal lumbar puncture, EEG and evidence of cerebral atrophy on CT or MRI.

**(III). Other clinical features consistent with a diagnosis of Probable AD, after exclusion of other causes of dementia other than AD include:**

**a.** Plateaus in clinical course

**b.** Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss

**c.** Other neurological abnormalities in some patients, especially with more advanced disease and including motor signs such as increased motor tone, myoclonus, or gait disorder

**d.** Seizures in advanced disease

**e.** CT normal for age.

**(IV). Features that make the diagnosis of Probable AD unlikely or uncertain:**

**a.** Sudden apoplectic onset

**b.** Focal neurological findings such as hemiparesis, sensory loss, visual field deficits and incoordination early in the course of the illness

**c.** Seizures or gait disturbances at the onset or very early in the course of the illness.

**(V). Clinical diagnosis of Possible AD:**

**a.** May be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric,

or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation or in the clinical course

**b.** May be made in the presence of a second systematic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia

**c.** Should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

***Table 1.1: Clinical criteria for the diagnosis of probable, possible and definite Alzheimer's disease***

The loss of cognitive abilities is often accompanied by a deterioration in emotional control, social behaviour and motivation. In the population-based Cache County Study in the USA (Lyketsos *et al.,* 2000), 61% of people with dementia had exhibited one or more behavioural or psychological disturbances in the past month. Apathy (27%), depression (24%) and agitation/aggression (24%) were the most common symptoms, and these were approximately four times more common in those with dementia than in those without this condition.

### 1.1.5 Assessment

Assessment of dementia requires a set of skills and knowledge that spans several clinical domains. The clinician should be familiar with normal aging, brain anatomy and brain pathology that produces dementia, and common disorders that mimic dementia. According to the Nice Guidelines for dementia (NICE, 2006) the diagnosis

of dementia should be made only after a comprehensive assessment, which should include:

- History taking
- Cognitive and mental state examination
- Physical examination and other appropriate investigations
- A review of medication in order to identify and minimise the use of drugs, including over-the-counter products that may adversely affect cognitive functioning.

A number of cognitive instruments have proven useful for screening individuals at risk for dementia. The Mini Mental State Examination (MMSE) (Folstein *et al.*, 1975) is the most commonly administered psychometric screening assessment of cognitive functioning. The MMSE is used to screen individuals for cognitive impairment, track changes in cognitive functioning over time and often to assess the effects of therapeutic agents on cognitive function (Strauss *et al.*, 2006).

The MMSE provides a brief evaluation of the cognitive domains affected in Alzheimer's disease, including orientation, registration, attention, recall, language and constructional praxis (Folstein *et al.*, 1975). MMSE scores range from 0-30, with low scores indicating greater cognitive impairment. Scores less than 24, are conventionally interpreted as evidence of a dementing illness. Performance on the MMSE is moderated by demographic variables, with scores decreasing with advanced age and lower levels of education (Lezak *et al.*, 2004). The MMSE has been demonstrated to be a relatively sensitive marker of overt dementia (Grut *et al.*, 1993; Mungas *et al.*, 1996; Harvan & Cotter, 2006).

Every individual with suspected dementia should undergo a thorough physical examination which should include a neurology evaluation. Medical illnesses that can result in dementia include thyroid disease, atherosclerotic vascular disease, collagen-vascular diseases (such as systemic lupus erythematosus) and infections. Where feasible, individuals with a clinical dementia syndrome should undergo structural brain imaging with non-contrast computed tomography (CT) or magnetic resonance imaging (MRI) to evaluate for focal lesions, deep white matter ischemic changes and regions of atrophy.

## 1.2 Neuroimaging of Alzheimer's disease

### 1.2.1 Magnetic Resonance Imaging (MRI)

Neuroimaging is an important tool in the preclinical detection and monitoring of Alzheimer's disease. MRI has emerged as a useful neuroimaging tool in the investigation of Alzheimer's disease on account of its relative safety and tolerability, and its ability to delineate individual structures in the brain. MRI provides an excellent tool for non-invasively observing structural change in vivo. The majority of Alzheimer's disease neuroimaging research to date has focused on MRI volumetry, which involves the measurement of brain regional volumes for the detection of atrophy.

A large portion of the MRI-based volumetric studies of Alzheimer's disease in the general population have focused on medial temporal structures which have been

implicated in the early stages of Alzheimer's disease (Kesslak *et al.*, 1991; Jack *et al.*, 1992; Lehericy *et al.*, 1994; Laakso *et al.*, 1995; Juottonen *et al.*, 1998; Du *et al.*, 2001; Killiany *et al.*, 2002; Pennanen *et al.*, 2004; Rusinek *et al.*, 2004). These findings have led to the suggestion that regional volumetry can be used as a diagnostic tool in the investigation of Alzheimer's disease.

Several longitudinal studies of Alzheimer's disease reported increased atrophy rates for the entorhinal cortex (Du *et al.*, 2003; Schott *et al.*, 2003), hippocampus (Kaye *et al.*, 1997; Jack *et al.*, 1998; 2000), corpus callosum (Teipel *et al.*, 2002) and global brain (Fox *et al.*, 1996; 1999a; Chan *et al.*, 2001). These findings suggest that accelerated brain atrophy is a characteristic feature of Alzheimer's disease, therefore distinguishing this disorder from normal aging.

The hippocampus is a central component of the medial temporal lobe memory system and its' structural and functional integrity is necessary for declarative memory (Squire & Zola-Morgan, 1991). People with mild to moderate Alzheimer's disease have a significant reduction in the volume of the hippocampus and associated cognitive deficits as compared to healthy controls (Kesslak *et al.*, 1991; Jack *et al.*, 1992). Hippocampal volumes have been consistently shown to be reduced by as much as 40% in people with clinically diagnosed Alzheimer's disease of moderate severity (Seab *et al.*, 1988; Kesslak *et al.*, 1991; Jack *et al.*, 1992). Hippocampal asymmetry has been reported to be present in older adults with subjective memory symptoms (Van der Flier *et al.*, 2004), mild cognitive impairment (Yamaguchi *et al.*, 2002) and Alzheimer's disease (Geroldi *et al.*, 2000). This finding suggests that age and degenerative processes do not necessarily affect the brain equally across hemispheres.

The amygdala has been shown to have greater accuracy than the hippocampus for discriminating mild Alzheimer's disease from healthy controls in a small number of isolated studies. These studies however were limited by a small sample size (Cuenod *et al.,* 1993; Lehericy *et al.,* 1994) or inadequate selection criteria (Krasuski *et al.,* 1998). The overall accuracy for amygdala atrophy ranged from 58-95%, which would suggest that amygdala is less efficient than hippocampal volume to discriminate mild Alzheimer's disease from healthy control subjects. Accuracy may however be enhanced by a combination of the amygdala and hippocampal volumes by means of investigating the amygdalo-hippocampal complex (Lehericy *et al.,* 1994; Pantel *et al.,* 2001; Hampel *et al.,* 2002).

Juottonen *et al.* (1999) used volumetric MRI imaging to compare the extent of atrophy of the entorhinal cortex and the hippocampus between individuals with Alzheimer's disease and control subjects. Subjects with Alzheimer's disease were shown to have significantly smaller volumes of the entorhinal cortex and hippocampus bilaterally. Compared with control subjects, the volume of the entorhinal cortex in individuals with Alzheimer's disease was 40% smaller on the left and 38% smaller on the right. The volume decrease in the hippocampus was 35% and 33% respectively. In the discriminant function analysis, volumetry of the entorhinal cortex yielded a specificity of 94% with a sensitivity of 90% in distinguishing Alzheimer's disease individuals from control subjects.

Du *et al.* (2004) measured the rate of atrophy of the entorhinal cortex and the hippocampus in people with Alzheimer's disease and control subjects. Atrophy rates of the entorhinal cortex and the hippocampus were found to be comparable in

differentiating between Alzheimer's disease and control subjects. However, in Alzheimer's disease individuals, the atrophy rate of the entorhinal cortex was significantly greater than that of the hippocampus. The hippocampi in Alzheimer's disease were 27% smaller on the left and 26% on the right. The entorhinal cortex was 38% smaller on the left and 40% smaller on the right. Furthermore, increased atrophy rates of both the entorhinal cortex and the hippocampus were correlated with increased memory deficits in mild Alzheimer's disease.

Xu *et al.* (2000) compared the usefulness of MRI measures of the entorhinal cortex versus the hippocampus in Alzheimer's disease. Despite the theoretical rationale for the superiority of entorhinal measurements in early Alzheimer's disease, the authors found that MRI measurements of the hippocampus and the entorhinal cortex were approximately equivalent at discriminating between subjects with Alzheimer's disease, mild cognitive impairment and healthy controls.

Several neuroimaging studies have shown that measures of generalised atrophy (e.g. CSF spaces) or regional atrophy (e.g. hippocampal loss) are associated with a clinical or histopathologic diagnosis of Alzheimer's disease. Rusinek *et al.* (2004) showed that the increased annual atrophy rate in the medial temporal lobe was a potential diagnostic marker for the progression of Alzheimer's disease. The study conducted by Chan *et al.* (2001) revealed widespread symmetrically distributed cerebral volume loss in Alzheimer's disease and contrasted this with the situation in frontal frontotemporal dementia in which there was greater atrophy anteriorly, and in temporal frontotemporal dementia in which the atrophy rate was greatest in the left anterior cerebral cortex.

MRI studies of healthy adults which investigated the association between hippocampal volume and memory have produced conflicting results (Golomb *et al.,* 1994; Soininen *et al.,* 1994; Sullivan *et al.,* 1995; Raz *et al.,* 1998; Du *et al.,* 2003). The association between entorhinal cortex atrophy and memory decline has been demonstrated in healthy adults at increased risk for developing Alzheimer's disease (de Toledo-Morrell *et al.,* 2000; Du *et al.,* 2003; Rodrigue & Raz, 2004).

A number of studies have shown that atrophy increases with disease severity (Stout *et al.,* 1996; Jack *et al.,* 1997), determined using specific neuropsychometry or with global clinical measures such as the MMSE. Rates of change in several structural measures, including whole brain (Fox *et al.,* 1999a; Josephs *et al.,* 2008; Schott *et al.,* 2008, Sluimer *et al.,* 2008; 2010), entorhinal cortex (Cardenas *et al.,* 2009), hippocampus (Kesslak *et al.,* 1991; Laakso *et al.,* 1995; Jack *et al.,* 2004; Thompson *et al.,* 2004; Ridha *et al.,* 2008; Morra *et al.,* 2009) and temporal lobe volumes (Hua *et al.,* 2009, Ho *et al.,* 2010), as well as ventricular enlargement (Thompson *et al.,* 2004; Jack *et al.,* 2004, Taoka *et al.,* 2006; Ridha *et al.,* 2008), correlate closely with changes in cognitive performance, supporting their validity as markers of disease progression.

Lehtovirta *et al.* (1998) studied subjects with Alzheimer's disease at the early stage of the condition, and control subjects. Individuals with Alzheimer's disease had smaller volumes of hippocampi and amygdala compared with control subjects, and those with Alzheimer's disease homozygous for the ε4 allele had the most prominent volume loss in the medial temporal lobe structures.

The volume of the entorhinal cortex was measured by Juottonen *et al.* (1998). The most prominent atrophy of the entorhinal cortex was seen in subjects with Alzheimer's disease with the apoE ε4 allele. This difference was greatest for females, and correlated with a memory decline. Schmidt *et al.* (1996) found no significant differences in gross structural MRI measures which included sulcul and ventricular enlargement, although apoE ε4 allele subjects performed worse on neuropsychological testing. Reiman *et al.* (1998) reported hippocampal volume loss in apoE ε4 subjects without Alzheimer's disease that was associated with memory loss. Donix *et al.* (2010) found that a family history of Alzheimer's disease and apoE ε4 allele status were associated with a thinner cortex in the entorhinal region, subiculum and adjacent medial temporal lobe subfields.

A maternal family history of Alzheimer's disease has been shown to be associated with reduced glucose metabolism on positron emission tomography (Mosconi *et al.*, 2007) and with a more rapid metabolic decline in people with Alzheimer's disease, compared to control subjects (Mosconi *et al.*, 2009). Reduced temporal lobe activity was demonstrated using functional magnetic resonance imaging (fMRI) among apoE ε4 carriers with a family history of Alzheimer's disease (Johnson *et al.*, 2002; Trivedi *et al.*, 2006). Memory tasks were shown to produce increased activation of the hippocampus in apoE ε4 carriers relative to non-carriers (Bookheimer *et al.*, 2000).

In mild cognitive impairment, neuroimaging can facilitate diagnosis and help to identify those people who are at risk of developing Alzheimer's disease (Jack *et al.*, 2005). MRI-based hippocampal volumetric studies can be used to distinguish Alzheimer's disease and mild cognitive impairment from healthy controls, with mild

cognitive impairment demonstrating hippocampal volumes smaller than healthy controls and larger than Alzheimer's disease (Grundman *et al.*, 2004; Pennanen *et al.*, 2004).

Longitudinal MRI studies have shown that atrophy rates predict conversion of mild cognitive impairment and normal cognitive function to Alzheimer's disease. As the severity of the hippocampal atrophy increases, the annual progression rate to Alzheimer's disease increases (Jack *et al.*, 1999; Cardenas *et al.*, 2003). Atrophy of other limbic structures such as the entorhinal cortex and/or parahippocampal gyrus (Convit *et al.*, 1997; Xu *et al.*, 2000; De Santi *et al.*, 2001; Dickerson *et al.*, 2001; Du *et al.*, 2001; Killiany *et al.*, 2002), amygdala (Fischl *et al.*, 2002) and cingulate cortex (Killiany *et al.*, 2000; Fox *et al.*, 2001), may also be associated with mild cognitive impairment.

Much attention has focused on volumetric MRI studies to investigate changes occurring early in Alzheimer's disease. Manual methods are typically Region of Interest (ROI) studies which tend to focus on a few specific brain regions which are well established as being affected in Alzheimer's disease such as in the entorhinal cortex or the hippocampus (Van Hoesen *et al.*, 1995; De Leon *et al.*, 1997; Mori *et al.*, 1997; Krasuski *et al.*, 1998; De Toledo-Morell *et al.*, 2000). ROI methods are often used when the investigators have *a priori* hypotheses and therefore, assessments are confined to a limited set of brain regions. These methodologies are in concept simple and are carried out for instance by manually tracing the structures or regions-of-interest on conventional MRI or alternatively, via semi-automated techniques such as stereology where a 3-D grid of fixed dimensions is placed on the entire brain and

subsequently the volumes of structures of interest are calculated by the manual marking of pixels falling within each 2-D slice of the structure of interest by a rater. The volume of the structure of interest which corresponds to the total number of marked pixels is then automatically calculated by computer software.

Automatic techniques have been developed to study more widespread brain volume and thickness measures (Fischl *et al.,* 1999; Dale *et al.,* 1999; Fischl & Dale, 2000). Studies of cortical thickness have demonstrated thinning in distributed association areas, suggesting that regional atrophy can be detected across widespread cortical regions (Lerch *et al.* 2005; Du *et al.* 2007). Dickerson *et al.* (2009) demonstrated abnormal cortical anatomy in Alzheimer's disease which paralled known regional vulnerability to Alzheimer's disease neuropathology.

### 1.2.2 Proton Magnetic Resonance Spectroscopy ($^1$H-MRS)

Proton Magnetic Resonance Spectroscopy ($^1$H-MRS) is a non-invasive method to investigate the concentrations of a number of brain metabolites including N-acetylaspartate (NAA), myo-inositol (mI), choline (Cho) and creatine plus phosphocreatine (Cr+PCr). $^1$H-MRS is unique among diagnostic imaging modalities because the signals from several different metabolites are measured within a single examination period. Each metabolite in turn is sensitive to a different aspect of in vivo pathologic processes at the molecular or cellular level.

N-acetyl aspartate (NAA) is the most abundant metabolite visible by $^{1}$H-MRS in the healthy human brain and is present almost exclusively in the nervous system (Birken *et al.,* 1989). NAA is hypothesized to be a marker of the number of viable neurons (Meyerhoff *et al.,* 1993), but also may reflect mitochondrial dysfunction (Bates *et al.,* 1996). NAA is reduced in both the cortical grey matter and in the white matter in people with Alzheimer's disease (Kantarci *et al.,* 2007). The regional decrease in cortical NAA level is in agreement with the regional neuropathological involvement in Alzheimer's disease (Kantarci *et al.,* 2007).

Myo-inositol (mI) affects neuronal development and survival, cellular osmolarity, membrane metabolism, signal transduction, protein C activation (Nishizuka, 1988) and amyloid deposition (Larrieu *et al.,* 2002). mI is increased in the grey matter of people with Alzheimer's disease. No significant mI changes have been confirmed in white matter, but a moderate inverse association between frontal white matter mI levels and global mental function have been recorded (Parnetti *et al.,* 1997).

Increased mI within temporal-parietal regions (Chantal *et al.,* 2004) and reduced NAA within hippocampal regions (Block *et al.,* 2002; Kantarci *et al.,* 2004) have been reported in people with Alzheimer's disease in the general population. The few studies of older adults with mild cognitive impairment found that they also had increased mI (Kantarci *et al.,* 2000) and reduced NAA (Chantal *et al.,* 2004) within temporal regions.

Choline (Cho) is a marker of membrane synthesis and degradation and has been found to be elevated in Alzheimer's disease in some (Christiansen *et al.,* 1993; Meyerhoff *et*

*al.,* 1994; MacKay *et al.,* 1996; Lazeyras *et al.,* 1998; Meyerhoff *et al.,* 1994; Pfefferbaum *et al.*, 1999; Kantarci *et al.,* 2004), but not all studies (Christiansen *et al.,* 1993; Miller *et al.,* 1993; Moats *et al.,* 1994; Ernest *et al.,* 1997; Heun *et al.,* 1997; Parnetti *et al.,* 1997; Schuff *et al.,* 1997; Rose *et al.,* 1999; Krishnan *et al.,* 2003). Elevated Cho in Alzheimer's disease has been attributed to increased membrane turnover due to neurodegeneration (Kantarci *et al.*, 2007). Increased Cho has also been postulated to be the consequence of membrane phosphatidylcholine catabolism in order to provide free choline for the chronically deficient acetylcholine production in Alzheimer's disease (Wurtman *et al.,* 1985; Ernst *et al.,* 1997).

Creatine plus phosphocreatine (Cr+PCr) reflects high energy phosphate metabolism and has been reported in many studies to remain stable in Alzheimer's disease (Moats *et al.,* 1994; Shonk *et al.*, 1995; Ernst *et al.,* 1997; Mohanakrishnan *et al.,* 1997; Parnetti *et al.,* 1997; Schuff *et al.,* 1997, 1998; Pfefferbaum *et al.*, 1999; Schuff *et al.,* 2002) and other neurodevelopmental disorders. Elevated Cr levels in Alzheimer's disease has however been reported (Huang *et al.,* 2001; Petrovitch *et al.*, 2001).

The NAA/mI ratio is the primary measure to distinguish individuals with Alzheimer's disease from healthy controls. This measure has been demonstrated with a sensitivity of 57-90% and a specificity of 73-95% in different cohorts, using different $^{1}$H-MRS acquisition parameters in different regions of the brain (Shonk *et al.,* 1995; Ernest *et al.,* 1997; Petrovitch *et al.,* 2001; Kantarci *et al.,* 2002; Martinez-Bisbal *et al.,* 2004; Fernandez *et al.,* 2005; Zhu *et al.,* 2006). The NAA/mI ratio in Alzheimer's disease significantly correlates with MMSE scores (Rose *et al.,* 1999) and has been shown to significantly predict MMSE change 12 months later (Doraiswamy *et al.,* 1998).

The reductions in NAA levels and NAA/Cr ratios have predicted conversion from amnestic mild cognitive impairment to Alzheimer's disease (Braak & Braak, 1991; Bates *et al.,* 1996; Hugg *et al.,* 1996; Brooks *et al.,* 2000; Bendszus *et al.,* 2002; Modrego *et al.,* 2005, 2006; Metastasio *et al.,* 2006). mI has been reported to be increased in the parietal lobes of people with amnestic mild cognitive impairment (MacKay *et al.,* 1996; Kantarci *et al.,* 2000) and mild Alzheimer's disease (Huang *et al.,* 2001), while NAA/Cr levels are either mildly decreased or normal compared with healthy controls.

Magnetic resonance spectroscopy measurements of NAA/Cr and mI/Cr ratios correlate with neuropsychological measures of cognitive function in people with Alzheimer's disease (Kwo-On-Yuen *et al.,* 1994; Doraiswamy *et al.,* 1998; Schuff *et al.,* 1998; Rose *et al.,* 1999; Jessen *et al.,* 2000; Huang *et al.,* 2001; Kantarci *et al.,* 2002) and also in transgenic mouse models of Alzheimer's disease (Marjanska *et al.,* 2005).

A reduction in NAA/Cr ratio and an increase in mI/Cr ratio have been shown to be associated with higher Braak stage, higher neuritic plaque score and greater likelihood of Alzheimer's disease (Kantarci *et al.,* 2008). mI/Cr and NAA/Cr may be useful for predicting prodromal Alzheimer's disease in people with mild cognitive impairment, and monitoring individuals with prodromal Alzheimer's disease. Furthermore, in people with Alzheimer's disease, the NAA/mI ratio is decreased more in the parietal lobe grey matter than in frontal grey matter, in agreement with the regional distribution of the neurofibrillary pathology in Alzheimer's disease (Zhu *et al.,* 2006).

An inherent limitation of $^{1}$H-MRS is the lack of specificity of the observed changes for any disease. In addition to neurodegenerative disorders, a reduction of NAA has been reported in vascular (Wardlaw *et al.,* 1998; Capizzano *et al.,* 2000), metabolic (Rajanayagam *et al.,* 1997) and inflammatory diseases (De Stefano *et al.,* 2001). Several studies (Pioro, 1997; Block, 1998; Rose *et al.,* 1999) have therefore investigated those brain regions that specifically characterise the distribution of neuronal damage in an individual disease.

## 1.3 Down's syndrome

Down's syndrome is associated with trisomy of chromosome 21 and occurs in approximately 1 per 1,000 live births. It is the most common genetic cause for intellectual disability. Intellectual disability means a significantly reduced ability to understand new or complex information and to learn and apply new skills (impaired intelligence). This results in a reduced ability to cope independently (impaired social functioning) and begins before adulthood, with a lasting effect on development (World Health Organisation Website). People with Down's syndrome encounter an additional disease burden because they have a significantly increased risk for developing Alzheimer's disease in later life. The risk of developing Alzheimer's disease appears to be independent of living arrangement, degree of intellectual disability and gender (Prasher *et al.,* 1997); however other environmental factors in combination with underlying genetic vulnerability may increase the risk (e.g. smoking, cholesterol, head injury, parental age at the birth of the child and oestrogen levels in females) (Farrer *et al.,* 1997).

In the general population, approximately 10% of 65 year olds and 40% of 80 year olds develop symptoms of Alzheimer's disease (Evans *et al.,* 1989). In contrast, the incidence of Alzheimer's disease in people with Down's syndrome is estimated to be 3-5 greater than that of the general population. Many studies have addressed the issue of prevalence of Alzheimer's disease in Down's syndrome. The figures obtained vary from 7-50% (Zigman *et al.,* 1996) depending on the stringency of the criteria, the measures used and the specific populations tested.

Visser *et al.* (1997) followed 307 institutionalised people aged 10-72 years with Down's syndrome and found that 18% (N=56) developed symptoms of Alzheimer's disease at an average age of 56 years. Tyrrell *et al.* (2001) found a prevalence rate of 13.3% for Alzheimer's disease among a community-based population of 285 people with Down's syndrome.

At autopsy, the presence of Alzheimer-type neuritic plaques and neurofibrillary tangles have been reported in the brains of 7.5% of people with Down's syndrome as early as the second decade of life, with a rise in prevalence to 80% of cases by the fourth decade and 100% over 60 years of age (Mann, 1988).

A significant proportion of the increased genetic risk for Down's syndrome individuals to develop dementia is probably explained by having trisomy of genes carried on chromosome 21 that are implicated in Alzheimer's disease. Hence, it has been hypothesised that the presence of an extra copy of the amyloid precursor protein (APP) gene in Down's syndrome individuals leads to increased formation of amyloid plaques, neuronal death and clinical Alzheimer's disease (Prasher *et al.,* 1998; Folin

*et al.,* 2003). Similarly trisomy of the mI transporter protein (Beacher *et al.,* 2005) is associated with an increase in brain mI, a compound which affects neuronal development and survival, cellular osmolarity, membrane metabolism, signal transduction, protein C activation (Giesel *et al.,* 2006) and amyloid deposition (McLaurin *et al.,* 1998). It has therefore been suggested that increased brain mI concentration may be related to cognitive impairment in Down's syndrome (Galdzicki *et al.*, 2001).

It has been previously reported (Beacher *et al.*, 2005) that non-demented people with Down's syndrome have a significant increase in the concentration of mI as compared to controls and that increased mI is associated with reduced overall cognitive ability (including memory). Furthermore, increased mI may predispose people with Down's syndrome to the later development of Alzheimer's disease, possibly mediated by the promotion of β-amyloid plaques (Beacher *et al.*, 2005).

These Down's syndrome specific vulnerability factors may also combine with the additional burden of having a lower cognitive reserve due to pre-existing intellectual disability. The concept of brain reserve refers to the ability of the brain to tolerate the pathology of age- and disease-related changes without obvious clinical evidence (Katzman *et al.,* 1988). The greater the reserve, the more severe pathological changes are needed to cause clinical functional impairment (Katzman, 1988; Setern, 2002; Stern, 2006). The cognitive reserve model suggests that the brain actively attempts to cope with brain damage by using pre-existing cognitive processing approaches or by enlisting compensatory ones (Setern, 2002).

Greater cognitive reserve can arise through numerous mechanisms, but is generally increased in people with higher overall intelligence and/or those able to more efficiently/flexibly use brain networks (Melzer *et al.,* 1997). Dementia risk has repeatedly been reported to be much lower in high-reserve individuals, but much higher in people with limited education and/or intellectual disability - a finding replicated across more than 20 studies involving more than 29,000 individuals and over a median follow-up period of greater than 7 years (McKhan *et al.,* 1984). Hence, it may be that dementia in people with Down's syndrome is associated with less loss of brain tissue than in the general population because they have less cognitive reserve due perhaps to a 'double hit' of prexisting intellectual disability combined with a genetically determined increase in risk factors such as brain amyloid and mI concentration.

There are two strategies that can be adopted in order to establish a decline in cognitive functioning in Down's syndrome (McQuillan *et al.*, 2003):

- A retrospective strategy which involves making an estimation of the individual's previous level of functioning from records, past test results and informants. This type of assessment can have poor reliability.
- A prospective strategy which involves assessing the individual using standardised measures to gain a baseline level of functioning and then repeating assessments to establish whether decline is occurring. This method is increasingly recommended as the approach of choice for people with intellectual disabilities (Oliver, 1999).

Due to the higher risk of Alzheimer's disease in Down's syndrome and the earlier onset, it is advisable to regularly assess a person's various skills, establishing a baseline assessment so that it is possible to identify changes in ability sooner rather than later. Good practice guidance from the Foundation for People with Learning Disabilities (Turk *et al.*, 2001) recommended that every service for people with intellectual disabilities should conduct a baseline assessment of cognitive and adaptive functioning before the age of 30 years. Burt & Aylward (2000) and Nieuwenhuis-Mark (2009) recommended annual cognitive screening for people with Down's syndrome over the age of 35 years. Carr (2000) demonstrated stability in intellectual ability and daily living skills for her cohort of people with Down's syndrome over the age period 21-30 years. This suggests that a baseline conducted in the 20s would capture people post-maturity and prior to any cognitive decline.

Unless a baseline is established when the person is healthy, it is very difficult to determine whether there has been a deterioration later in life. By the time an individual is referred with concerns, considerable deterioration may have occurred and an accurate account of premorbid function may be difficult to construct. Furthermore, an accurate and extensive record of baseline skill and cognitive levels in people with Down's syndrome is crucial and regular comparison with baseline is key to early diagnosis of dementia (Jethwa & Cassidy, 2010) and to enhance the sensitivity and specificity of the subsequent Alzheimer's disease diagnosis. However, in many areas reactive assessment is provided for those with signs of deterioration, with limited baselines and prospective screening such as that described by McBrien *et al.* (2005) being provided to all young adults with Down's syndrome.

In order to assess cognitive functioning in the Down's syndrome population, a wide variety of tests have been used including the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) and the Cambridge Cognitive Examination (CAMCOG) (Roth *et al.,* 1999). The CAMCOG has been validated for use with Down's syndrome adults (Hon *et al.,* 1999) and provides a measure of general cognitive function, including measures of memory, orientation, language, attention, praxis and executive function. The CAMCOG is appropriate for assessing cognitive function in people with intellectual disability, unlike more standard tests of cognitive function such as the Weschler Adult Intelligence Scales. The CAMCOG incorporates, and is highly correlated with, the MMSE (Blessed *et al.,* 1991).

CAMCOG scores are very effective in differentiating between demented and non-demented individuals (Roth *et al.,* 1999). Huppert *et al.* (1995) reported that the CAMCOG total score, as well as each subscale score, differed significantly between non-demented individuals and those with a diagnosis of mild dementia or minimal dementia (Roth *et al.,* 1999).

## 1.4 Neuroimaging of Down's syndrome

### 1.4.1 Magnetic Resonance Imaging (MRI)

In vivo MRI studies have investigated age related brain atrophy in Down's syndrome. Progressive cerebral atrophy and an increase in third ventricle size are inconsistently observed in older Down's syndrome individuals and are consistently associated with dementia (Schapiro *et al.,* 1989; LeMay *et al.,* 1990). It has been suggested that significant atrophy only becomes apparent when the clinical features of dementia have developed (Schapiro *et al.,* 1989).

Volumetric neuroimaging studies of adults with Down's syndrome (Lott & Lai, 1982; Schapiro *et al.,* 1989; Devinsky *et al.,* 1990; LeMay & Alvarez, 1990; Pearlson *et al.,* 1990; Schapiro *et al.,* 1992; Krasuski *et al.,* 2002) have revealed smaller overall brain volumes than would be expected from aging alone, with disproportionately smaller volumes of the cerebellum, brainstem, frontal lobe, amygdala, posterior parahippocampal gyrus and hippocampus. The amygdala and hippocampal volumes have been shown to be positively correlated with memory measures (Krasuski *et al.,* 2002). Basal ganglia volumes however, have been reported to be normal in MRI volumetric studies of adults with Down's syndrome (Raz *et al.,* 1995; Aylward *et al.,* 1997). A commonly recognised feature of the brains of subjects with Down's syndrome is a narrow superior temporal gyrus (Burger *et al.,* 1973; Becker *et al.,* 1986; Wisniewski *et al.,* 1990).

Volumetric MRI studies of individuals with Down's syndrome that measured hippocampal volume have reported significant decreases in volumes compared with healthy controls (Jernigan *et al.,* 1993; Kesslak *et al.,* 1994; Raz *et al.,* 1995), even before any signs of cognitive impairment. Reduced hippocampal volume is not however a feature of all subjects with an intellectual disability. In individuals with fragile X syndrome (Reiss *et al.*, 1994) and autism (Groen *et al.,* 2010) for example, hippocampal volume has been shown to be significantly increased compared to healthy controls. Reductions in hippocampal volume in Down's syndrome have been reported to be significantly positively correlated with memory abilities in healthy adults with Down's syndrome (Krasuski *et al.,* 2002).

In studies of non-demented individuals with Down's syndrome which investigated the relationship between hippocampal volume and age, no significant correlation (Raz *et al.,* 1995; Aylward *et al.*, 1999) and a negative correlation (Kesslak *et al.,* 1994) have been reported. Hippocampal volume may remain stable up to the age of 50 years in non-demented subjects with Down's syndrome (Aylward *et al.*, 1999). The reduction in hippocampal volume after age 50 years might be associated with a conversion to dementia.

Amygdala volumes in non-demented subjects with Down's syndrome have also been shown to remain constant during development (Aylward *et al.*, 1999). The atrophy of the amygdala in later life, as in the case of the hippocampus, has been suggested to signify involvement in the dementia process (Aylward *et al.*, 1999).

Cross-section studies of non-demented Down's syndrome subjects have shown increased ventricular volume with age (Ikeda & Arai, 2002; Kesslak *et al.,* 1994). Age related reductions of overall cerebral total and grey matter volumes have not however been detectable before the onset of dementia (Schapiro *et al.,* 1989, 1992; Kesslak *et al.,* 1994; Raz *et al.,* 1995). Volumetric studies with MRI have described decreased total cortical grey matter volume with increasing age in Down's syndrome subjects only after the onset of dementia (Schapiro *et al.*, 1989, 1992; Kesslak *et al.* 1994; Raz *et al.,* 1995).

Voxel based morphometry may be more sensitive than volumetric studies for demonstrating reductions of neocortical grey matter in the predementia stage of Down's syndrome.White *et al.* (2003), Teipel *et al.* (2003) and Teipel *et al.* (2004) demonstrated a reduction of grey matter with increasing age in neocortical association areas in non-demented subjects with Down's syndrome using MRI and voxel based morphometry. In a study comparing subjects with Down's syndrome to matched normal controls using voxel-based morphometry to determine regional gray and white matter volumes, the Down's syndrome group showed less gray matter in the cerebellum, anterior cingulate, frontal lobe and temporal lobe, including part of the hippocampus. Increased gray matter compared to controls was also demonstrated in the parahippocampal gyrus and in the inferior brainstem (White *et al.,* 2003).

One post mortem study described reduced grey matter volume in posterior cortical areas correlated with neurofibrillary tangle and neuritic plaque load in Down's syndrome subjects (de la Monte & Hedley-Whyte, 1990). These findings suggest that

regional grey matter reductions in Down's syndrome subjects reflect reductions of neuron density due to Alzheimer's disease type pathological changes.

Five volumetric MRI studies compared whole brain anatomy in Down's syndrome individuals with and without dementia (Kesslak *et al.,* 1994; Pearlson *et al.,* 1998; Aylward *et al.,* 1999; Prasher *et al.,* 2003; Beacher *et al.,* 2009). These studies reported that compared to non-demented Down's syndrome controls, those with dementia have a significant reduction in the volume of the medial temporal lobe/hippocampus, in addition to a significant enlargement of the ventricular cerebrospinal fluid (Kesslak *et al.,* 1994; Pearlson *et al.,* 1998; Beacher *et al.,* 2009). The study undertaken by Beacher *et al.* (2009) compared whole brain anatomy, as measured by volumetric MRI in Down's syndrome individuals with and without dementia. Down's syndrome individuals with dementia had significantly smaller corrected volumes bilaterally of the hippocampus and caudate, and right amygdala and putamen, in addition to a significantly larger corrected volume of the left peripheral cerebrospinal fluid compared to Down's syndrome individuals without dementia. Down's syndrome subjects with dementia had significantly lower scores on most cognitive measures, compared to healthy Down's syndrome individuals.

### 1.4.2 Magnetic Resonance Spectroscopy ($^1$H-MRS)

There have been few previous studies of subjects with Down's syndrome using $^1$H-MRS. Most authors have conducted measurements of the respective metabolites in the

hippocampal region, in the basal ganglia, and in the parietal and occipital lobes. There has been preliminary evidence that individuals with Down's syndrome may have an increase in brain mI concentration compared with controls (Shonk *et al.,* 1995; Berry *et al.,* 1999; Huang *et al.,* 1999).

The study undertaken by Beacher *et al.* (2005) found that hippocampal mI concentration was significantly higher in people with Down's syndrome compared to controls. Furthermore, in people with Down's syndrome, increased mI concentration was significantly negatively correlated with overall cognitive ability.

In the study conducted by Huang *et al.* (1999), the concentrations of mI and choline-containing compounds were shown to be significantly higher in the occipital and parietal regions of adults with Down's syndrome than in the comparison subjects. Within the Down's syndrome group, older subjects were shown to have higher mI levels than younger subjects. Older subjects in both groups had lower NAA than the respective younger subjects, although this old-young difference was not greater in the Down's syndrome group.

Murata *et al.* (1993) studied 18 people with Down's syndrome between 20-46 years of age, and aged matched healthy controls. In subjects with Down's syndrome, the ratios of Cho/Cr and NAA/Cho were shown to be significantly increased in those people in their 40s. They proposed that these changes were indicative of degeneration and/or rapid synthesis of brain cell membrane.

Berry *et al.* (1999) showed a significant increase in the mI level in the basal ganglia (striatum) in Down's syndrome children compared to the control group. A study of 14 children with Down's syndrome aged 7-17 years and 20 age-matched controls were investigated by Smigielska-Kuzia & Sobaniec (2007) to assess metabolic changes in the frontal lobes. The frontal lobes of the children with Down's syndrome showed reduced NAA/Cr, Glx/Cr, Cho/Cr and mI/Cr ratios. The differences between the ratios of the first two markers to creatine were statistically significant. However, no differences were found between GABA/Cr ratios in the two frontal lobes in subjects with Down's syndrome as compared to the control group.

## 1.5 Objectives and hypotheses

To my knowledge, no in vivo case-control study exists comparing the anatomy of dementia in Down's syndrome to people with Alzheimer's disease in the general population. Hence, it is unknown if the clinical symptoms of dementia in Down's syndrome are associated with similar anatomical differences from controls; for example similar differences in brain and/or medial temporal atrophy, as in non-Down's syndrome populations. Hence, I compared the volumes of the hippocampus, temporal lobes, lateral ventricles, whole brain volume, total cranial volume and additional more global cortical volume and thickness measures in Down's syndrome subjects with and without dementia to each other and to three non-Down's syndrome groups. These included one group of individuals with Alzheimer's disease and two groups of controls (each age-matched for their respective Down's syndrome and general population Alzheimer's disease cohorts).

I also compared the volumes of the hippocampus, temporal lobes, lateral ventricles, whole brain volume and total cranial volume in subjects with Alzheimer's disease, mild cognitive impairment and Alzheimer's disease healthy controls, scanned at baseline and re-scanned at 12 months.

I also examined metabolites in voxels of interest in the left and right hippocampi.

In this thesis, I tested the following hypotheses:

1. Subjects with dementia have a significant reduction in the volume of the hippocampus, temporal lobe and whole brain and an increase in the volume of the lateral ventricles, compared to their non-demented controls.
2. There is a significant correlation between atrophy of the hippocampus and temporal lobe, and cognitive decline.
3. Significant differences for more global volume and thickness measures exist between demented and non-demented subjects, and enables the distinction of subjects with Alzheimer's disease from demented subjects with Down's syndrome.
4. In a longitudinal study, when compared to age matched healthy controls, subjects with Alzheimer's disease have a significant reduction in the volume of the hippocampus and temporal lobe, and an increase in the volume of the lateral ventricles at baseline and when re-scanned at 12 months. Subjects with mild cognitive impairment have findings intermediate between those of Alzheimer's disease and age matched healthy controls.
5. Significant metabolite differences exist between demented and non-demented subjects.

# Chapter 2

# Methodology

## 2.1 General overview

Psychiatric illnesses are characterised by alterations in thinking, mood or behaviour (or some combination thereof), associated with significant distress and impaired functioning over an extended period of time. The symptoms of psychiatric illness vary from mild to severe, depending on the particular condition, the individual, the family and the socio-economic environment. Psychiatric illnesses cause enormous human suffering for individuals and their families and can impose major economic costs for the population. The incomplete understanding of psychiatric illnesses contributes to the stigma experienced by patients and influences the quality of service provision and availability of effective treatments.

The precise cause of most psychiatric illnesses is unknown. There is therefore an increasing need to research psychiatric disorders in order to enhance our overall understanding of these conditions. The assessment of the brain pathophysiology underlying psychiatric conditions constitutes a challenge and an opportunity for the techniques of human neuroimaging because they are well-placed to unravel the structural and functional correlates of psychiatric symptoms in the brain. Moreover,

they may reveal changes in information processing that precede the onset of the clinical disorder and thus provide markers of risk or prognosis.

Neuroimaging is being used more frequently to assist with the detection and diagnosis of psychiatric illness and to increase our understanding of the aetiology of these conditions. Neuroimaging can be used to study brain development in healthy subjects and in subjects with certain illnesses and to investigate disease progression and the effects of medications or other treatments on the brain.

Magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (H1-MRS) show significant promise in unravelling the aetiology of psychiatric disorders. These methods, while enhancing our understanding of causation, can also help in the potential identification of endophenotypes which are presently poorly described in psychiatric disorders. Ultimately, it is hoped that advances in the identification of such abnormalities may better assist in providing focused treatments in clinical practice.

## 2.2 Overview of MRI methodology

MRI uses the magnetic properties of hydrogen and its interaction with both a large external magnetic field and radio waves to produce highly detailed images of internal anatomy.

The hydrogen nucleus rotates upon itself in a 'spin' and because it is charged, it produces a small magnetic field, behaving like a tiny magnet. In the absence of an external magnetic field, the spin directions of all atoms are random and cancel each other. When placed in an external magnetic field, the spins align with the external field. By applying a rotating magnetic field in the direction orthogonal to the static field, the spins can be pulled away from the z-axis with an angle alpha. The bulk magnetisation vector rotates around z at the Larmor frequency (precess) which is calculated by the product of the gyromagnetic ratio with the strength of the magnetic field.

If a radiofrequency pulse is applied to the nucleus of an atom at the Larmor frequency, the protons will alter their alignment such that they become aligned with the orientation of the main magnetic field. In the case of hydrogen nuclei, they absorb radiofrequency energy and are said to be in a state of resonance (Filler, 2009). The precession relaxes gradually, when the xy-component reduces in time, the z-component increases. The xy component of the magnetisation vector produces a voltage signal which is the MRI signal which is measured.

## 2.3 Image acquisition

Subjects were scanned using a 1.5 Tesla, GE NU/i Signa MR System at the Maudsley Hospital in London. The GE Signa MR/i MR System is a short bore, high performance, whole-body imaging system operating at 1.5 Tesla. The system can image in any orthogonal or oblique plane (including single and double axis obliques),

using a wide variety of pulse sequences. A birdcage coil was used for RF transmission and reception. A vacuum fixation device ensured that subjects were both comfortable and restrained from movement during the scanning process. The whole brain was imaged with a three-dimensional (3-D) inversion recovery prepared fast spoiled gradient-recalled acquisition in the steady state (SPGR) T1-weighted dataset. These T1-weighted images were obtained in the axial plane with 1.5mm contiguous sections, repetition time (TR) of 13.8 milliseconds, inversion time (TI) of 450 milliseconds, echo time (TE) of 2.8 milliseconds and flip angle of 20° with one data average and a 256×256×124 matrix. Image contrast for all datasets was chosen with the aid of optimising software (Simmons *et al.*, 1996). Acquisition time was 6 minutes, 27 seconds.

## 2.4 Overview of MRI analytical methodology

Following post-processing, image analytical techniques may be applied to MRI images that are usually based on manual or computerised methodology. Usually after image acquisition and prior to image analysis, a set of further steps is required to prepare the MR images for computerised analysis. These may include scalp, skull and meningeal stripping, thereby leaving only the underlying brain intact for analysis. Additionally, the brain may be rotated to align it with a particular plane, e.g. anterior commisure-posterior commisure plane or the image brightness or contrast may be adjusted. These parameters may be adjusted manually or automatically depending on the image analysis protocol.

In the current study, before it was possible to study the brain images, head tilt adjustments were made to the MRI brain scans which had been processed and stored on a CD. The purpose of the head tilt adjustments were to ensure that measures taken from all the images were derived from a consistent angle and orientation.

The sagittal (left) view tilt correction was performed by aligning the bottom of the anterior commissure and the bottom of the posterior commissure of the corpus callosum (see Figure 2.1).

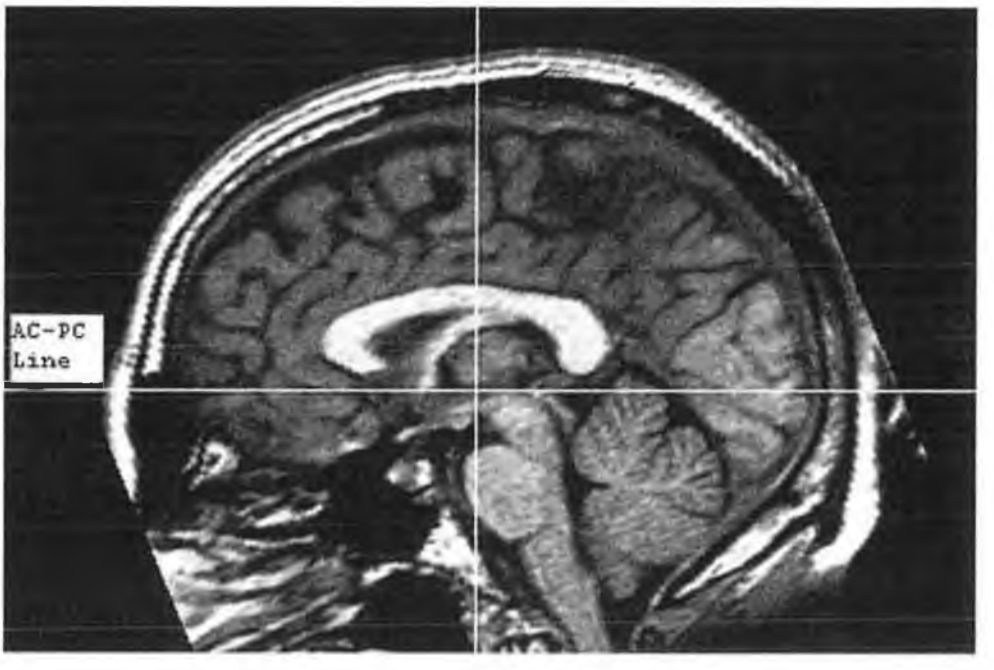


***Figure 2.1: Tilt correction in a sagittal view using crosshair alignment along the anterior commissure and posterior commissure line***

On completion of tilt adjustment in the sagittal plane, the alignment crosshair in the coronal (frontal) view was aligned to run through the longitudinal (inter-hemispheric) fissure, along the midline of the two hemispheres (see Figure 2.2).

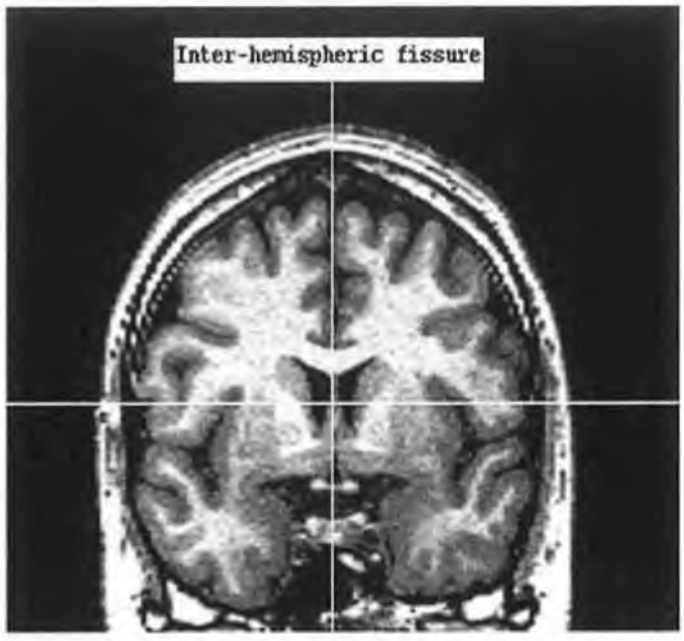


***Figure 2.2: Tilt correction in a coronal view using crosshair alignment along the inter-hemispheric fissure***

A final tilt was made for the axial view. The alignment crosshair was orientated to run through the midline of the two hemispheres (Figure 2.3).

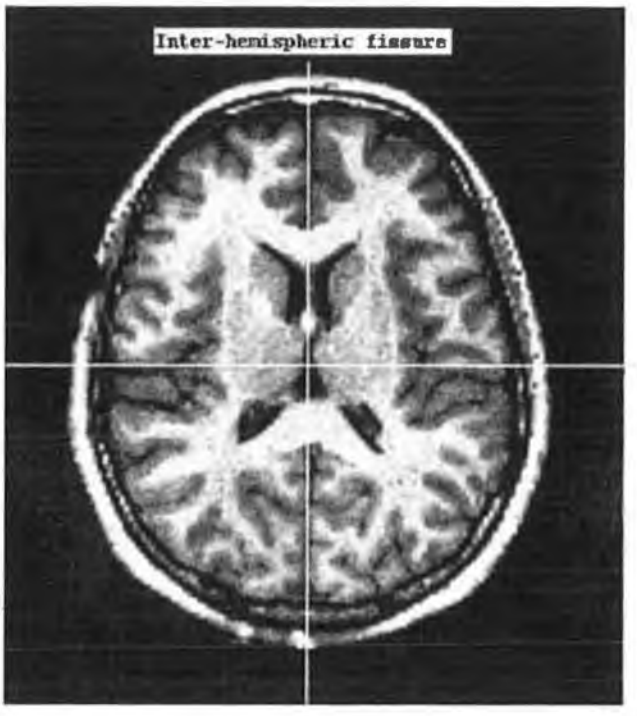


***Figure 2.3: Tilt correction in an axial view using crosshair alignment along the inter-hemispheric fissure***

## 2.5 Magnetic resonance imaging volumetric analysis

### 2.5.1 Region of interest manual tracing

The reformatted SPGR data set was analysed using Measure Software (Barta *et al.*, 1997). Measure is an image processing and analysis software programme which runs on Windows-based PC systems such as Windows 3.1 and Windows 95 operating systems. Stereology or 'proper sampling' can be used to obtain unbiased volume estimates by the application of the Cavalieri method, a mathematically unbiased method for geometric property estimation (Gundersen & Jensen, 1987). The programme currently allows for stereologically unbiased estimation of volume and has been validated by studies with MRI phantoms and in vivo studies (Roberts *et al.*, 1994, 2000).

Volumetric analysis of hippocampi, temporal lobes, lateral ventricles, whole brain and total cranial volumes were performed by means of manually tracing regions of interest (Murphy *et al.*, 1992, 1993a, 1993b). Region of Interest (ROI) studies are often used when the investigators have a priori hypotheses. Assessments are therefore confined to a limited set of brain regions. These methodologies are in concept simple and are carried out for instance by manually tracing the structures or regions-of-interest on conventional MRI or alternatively via semi-automated techniques such as stereology where a 3-D grid of fixed dimensions is placed on the entire brain and subsequently the volumes of structures of interest are calculated by the manual marking of pixels falling within each 2-D slice of the structure of interest by a rater. The volume of the

structure of interest which corresponds to the total number of marked pixels is then automatically calculated by computer software.

ROI tracing of the hippocampus is shown in Figure 2.4. The volume of each region was calculated by multiplying the summed pixel cross sectional areas by slice thickness.

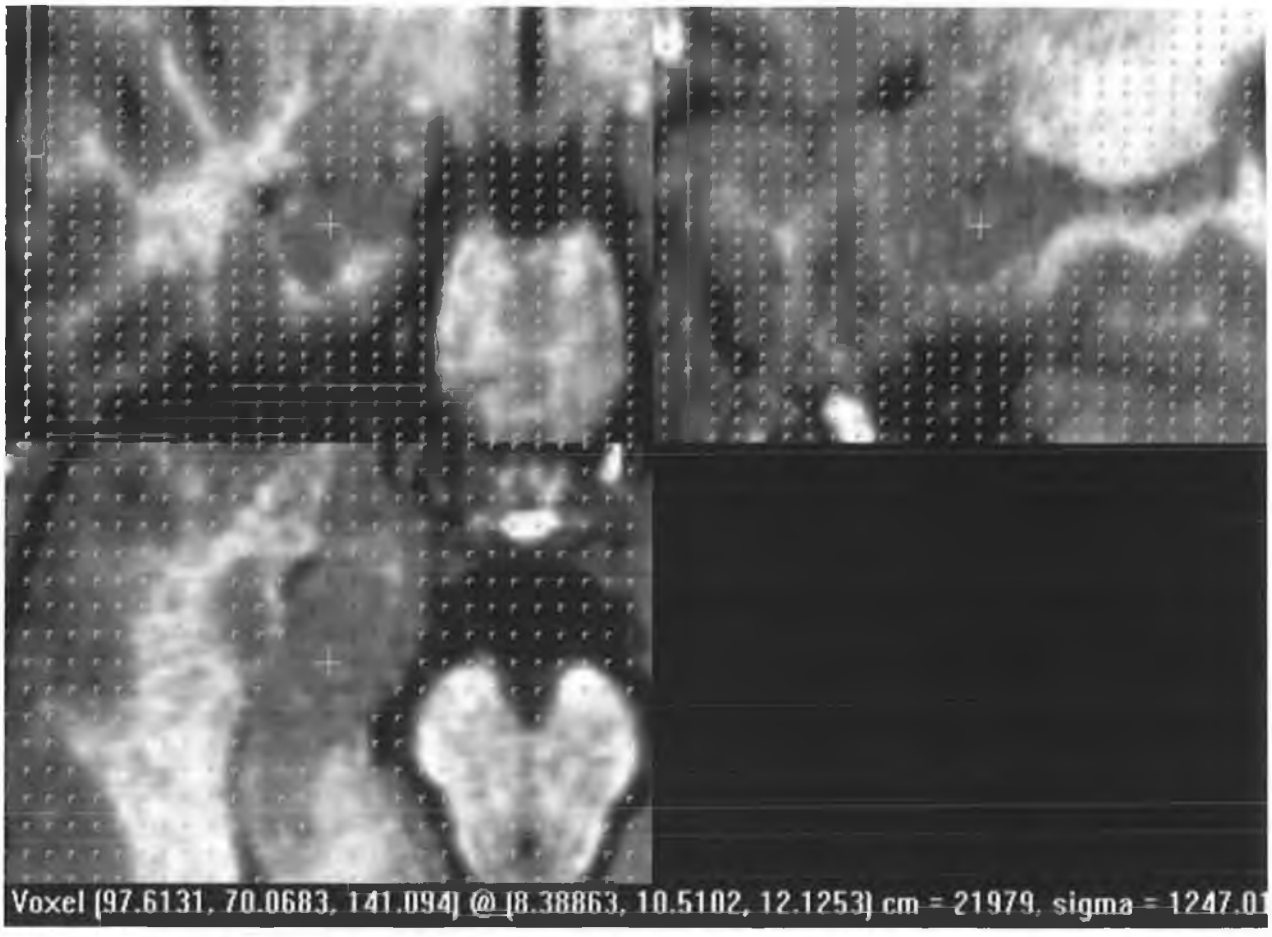


***Figure 2.4: Region of interest manual tracing of the hippocampus***

The hippocampal boundaries which were used for evaluating the ROI were:

- Posterior boundary - the fornix.
- Lateral boundary - the temporal horn of the lateral ventricle.
- Inferior boundary - the white matter of the parahippocampal gyrus.
- Superior boundary - the alveus.
- Mesial boundary - the mesial edge of the temporal lobe.
- Anterior boundary - the amygdala.

The temporal lobe boundaries which were used for evaluating the ROI were:

- Region 1 - everything frontal to the first slice in which the callosum connects the hemispheres.
- Region 2 - everything from the frontal-most corpus callosum to the last slice frontal to the thalamus.
- Region 3 - everything from the beginning of the thalamus up to and including the last slice (most posterior) in which the corpus callosum joins the hemispheres.
- Region 4 - everything caudal to the last slice in which the corpus callosum joins the hemispheres.

Cerebrospinal fluid, ventricles, cerebellum, and brain stem were excluded from temporal lobe region of interest studies.

The lateral ventricle boundaries which were used for evaluating the ROI were:

- Anterior boundary - the lateral ventricles extend forward into the frontal lobe as the interior horn.

- Main body - stretches from the intra-ventricular foramen posteriorally to the splenium of the corpus callosum.
- Posterior boundary - the posterior horn extending posteriorally into the occipital lobe.

The area to be marked for the ROI evaluation of whole brain volume was the entire brain excluding the ventricles, cerebrospinal fluid, cerebellum, dura matter and brain stem.

Intra-rater reliabilities were determined for the brain regions of interest traced by the operator (Dr Mullins) as part of this analysis. The rater (Dr Mullins) was blind to subject status. Highly significant intra-rater reliabilities were obtained in all cases. The intra-rater correlation co-efficient was $r > 0.9$ for all regions.

### 2.5.2 Subjects for volumetric analysis

In the current study, volumetric analysis was undertaken to compare subjects with Down's syndrome (DS) to those with Alzheimer's disease (AD) in the general population. Additional volumetric analysis was undertaken on MRI scans of subjects with AD, mild cognitive impairment (MCI) and Alzheimer's disease healthy controls (AD HC) at baseline and subjects who were re-scanned after 12 months.

## 2.6 Automated volume and thickness measurements

### 2.6.1 Surface-based stream

Cortical thickness measurements used a surface-based image processing pipeline developed by Fischl and Dale (Fischl *et al.*, 1999, Dale *et al.*, 1999). Firstly, the T1 weighted MRI volume was registered with the Talairach atlas (Talairach & Tournoux, 1988). The Talairach atlas was originally conceived to provide a standardised coordinate system for location of brain structures in stereotactic space and has been widely used in neuro-clinical procedures (Fox, 1997; Letovsky *et al.*, 1998; Lancaster *et al.*, 2000). Talairach normalisation consists of a linear transformation that converts the brain into a grid of 1,056 cells. These volume cells can be considered to represent homologous measuring units of volume or activity rates across subjects.

The high resolution T1 weighted images generated by an MR scanner are typically corrupted by magnetic susceptibility artifacts and RF-field inhomogeneities, resulting in variations in both intensity and contrast across the image. This is undesirable for any segmentation procedure which utilises intensity information in order to classify voxel data into different tissue types. The B1 bias field was estimated using variation in the white matter intensity in Talairach space and a correction for the B1 bias field was applied.

Automated skull stripping was performed on the intensity normalised data. This procedure involves deforming a tessellated ellipsoidal template into the shape of the inner surface of the skull (Dale *et al.*, 1999). Following the automated removal of the

skull (Segonne *et al.*, 2004), voxels were classified as white matter or non-white matter based on intensity and neighbour constraints. Cutting planes were chosen to isolate the hemispheres from each other, as well as to remove the cerebellum and brain stem. The location of the cutting planes was based on the expected Talairach location of the corpus callosum and pons, as well as several rule-based algorithms that encode the white matter mass for that hemisphere. An initial surface between white and grey matter for each hemisphere was generated and then refined. This white matter/grey matter surface was then expanded to identify the surface between grey matter and CSF (the pial surface). The distance between the white matter and the pial provided the thickness at each location of the cortex (Fischl & Dale, 2000).

Finally, an automated method for parcellating the cortical surface into a series of anatomical surface patches was applied (Fischl, 2004). Surface based labelling is shown in Figure 2.5.

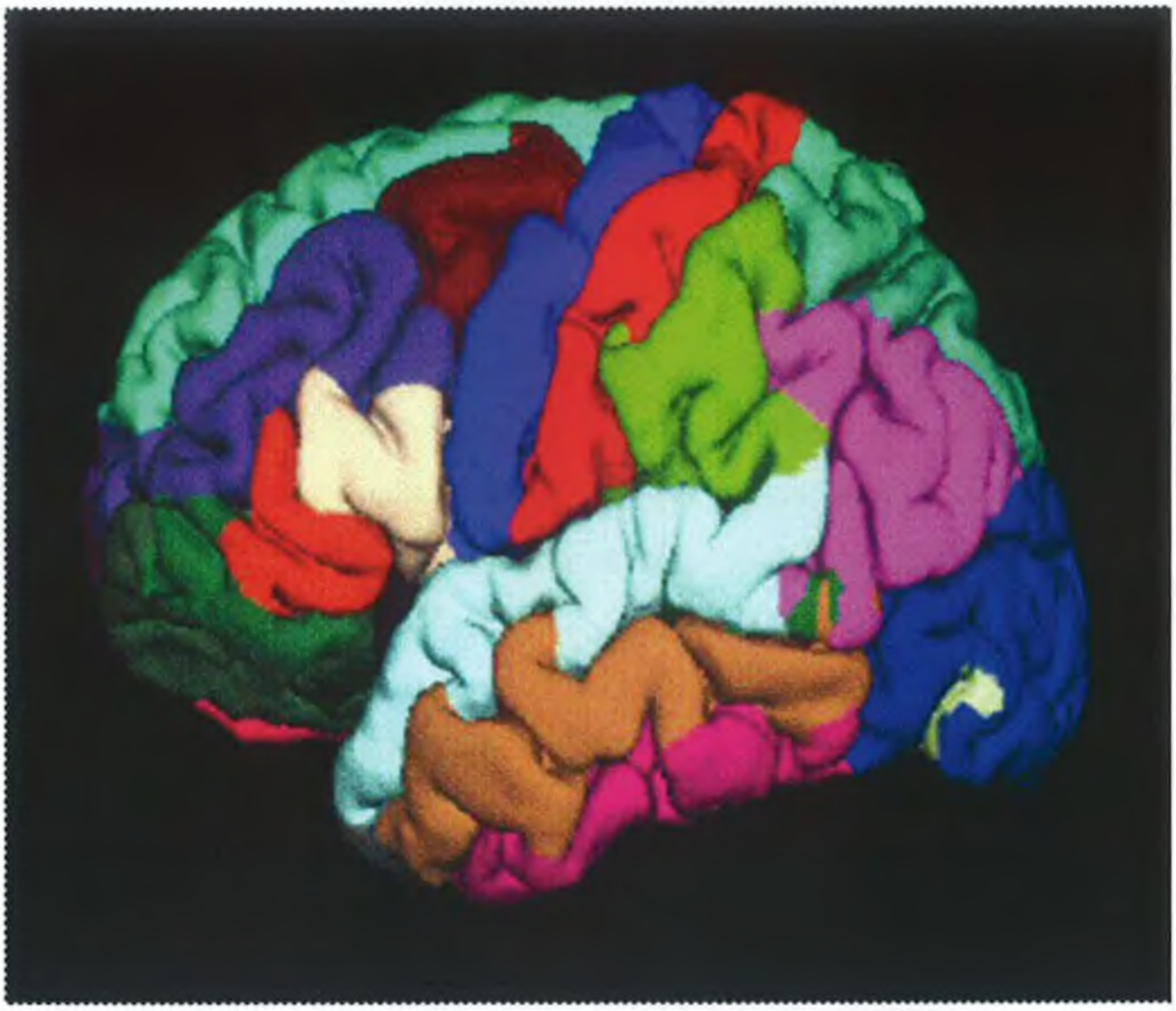

*Figure 2.5: Surface based labelling*

### 2.6.2 Volume-based stream

Morphometric changes associated with neurodegenerative disorders and normal aging include varations in the volume or shape of subcortical regions, in addition to alterations in the thickness, area and folding pattern of the cortex. While surface-based analysis investigates cortical variability, volumetric analysis is requred to detect changes in non-cortical structures. For surfaced-based labeling, the measured value is the curvature in each of the principal directions at that vertex. For volume-based labeling, the measured value is the intensity at that voxel.

Volumes of anatomical structures were determined using a volume-based image processing pipeline consisting of five stages (Fischl *et al.*, 2002, 2004). Affine registration was made to Talairach space designed to be insensitive to pathology and to maximise the accuracy of the final segmentation. The accuracy of the registration procedure can ultimately be assessed by examining the number of anatomical classes that occur at each atlas location. Ideally, all voxels should have only one anatomical class located at a particular atlas location. As the registration becomes less accurate, the number of anatomical classes occuring within an atlas voxel increases.

This next stage involved initial volumetric labelling. The B1 bias field was then corrected using a different technique from that used in the surface-based stream. This was followed by a high dimensional non-linear volumetric alignment to a Talairach atlas in order to achieve point-to-point correspondence for all subjects. A final segmentation step used subject-independent probabilistic atla to produce volume segmentations of anatomical structures.

In order to classify every point in space to a particular label for a given data set, it was necessary to identify the segmentation that maximised the probability of input given the prior probabilities from the training set. The probability of each class at each point was computed. Each point was allocated to the class for which the probability was greatest in order to achieve initial segmentation. The class probabilities were then re-computed. Re-segmentation was undertaken on this new set of class probabilities. This process was repeated until the segmentation was unaltered. The end result was a label for each point in space and an understanding of the probability of seeing the measured value at each voxel. Volume based labelling is shown in Figure 2.6.

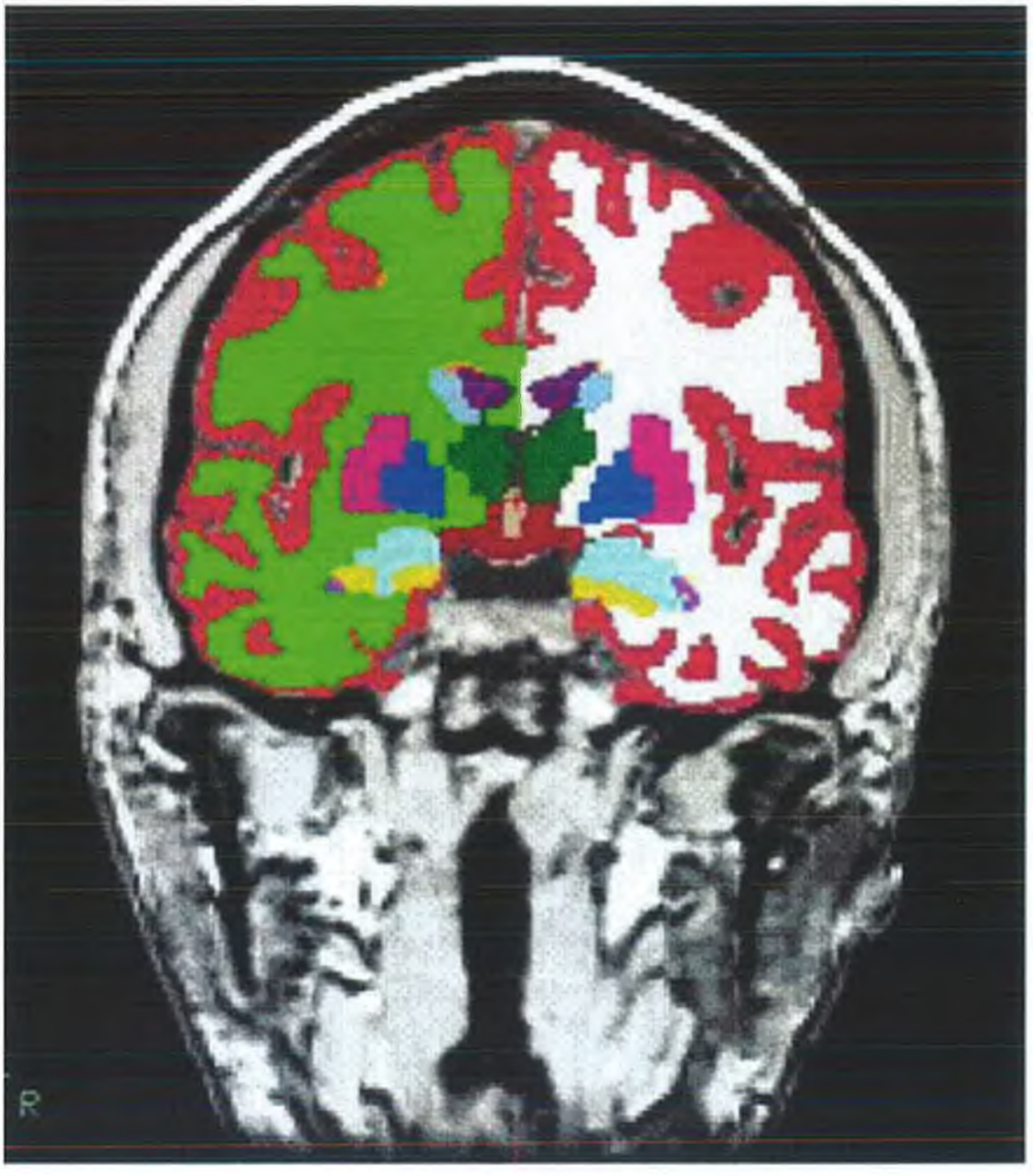

*Figure 2.6: Volume based labelling*

## 2.7 Magnetic resonance spectroscopy

### 2.7.1 Magnetic resonance spectroscopy protocol

Magnetic resonance spectroscopy (1H-MRS) voxels of interest (6mL) were defined in the left and right hippocampi. The anterior and posterior extents of the hippocampal/amygdala complex were initially defined from localiser images and a section of the axial 3-D inversion recovery prepared SPGR volume was then reoriented into the coronal plane for visualisation of the hippocampus (Figure 2.7). The anterior extent of the voxel was defined as the coronal slice where the amygdala disappeared, with the posterior extent 20mm from this. The centre of the voxel was denoted by the centre of the white matter tract in the superior/inferior and right/left positions. A point resolved spectroscopy (PRESS) pulse sequence (TE 35msec, TR 1500msec, 256 data averages, 2048 points) with automated shimming and water suppression was used to obtain spectra from each voxel with high signal to noise ratio and clearly resolved NAA, mI, Cr+PCr and Cho peaks among other metabolites.

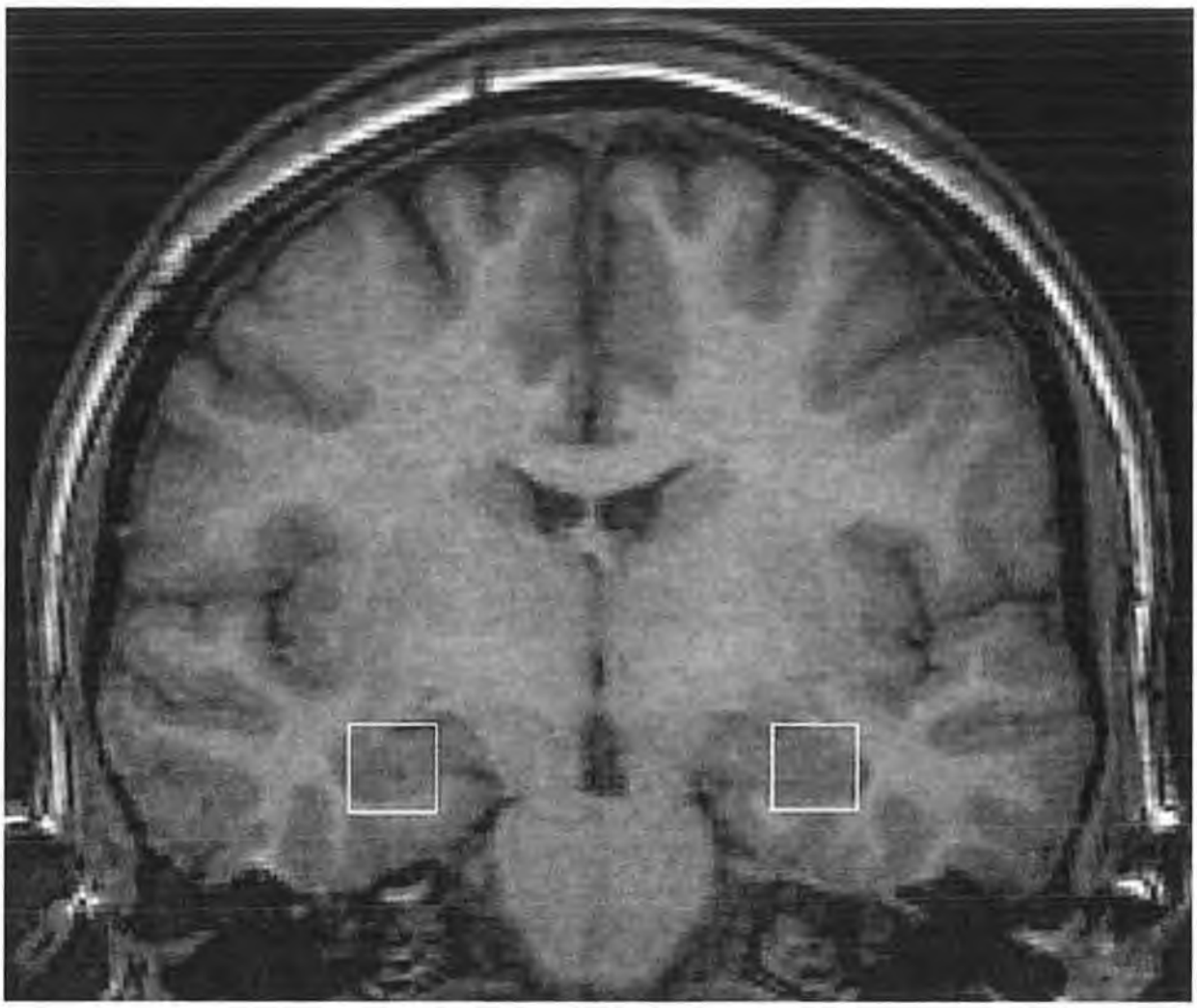

*Figure 2.7: Axial T1 weight MRI illustrating the locations of the 1H-MRS voxels in the left and right hippocampi*

Water suppression was carried out by a sequence of chemical shift selective (CHESS) radio frequency (RF) pulses to excite and associated spoiling gradients to dephase water before the localisation sequence. The flip angle of the last CHESS RF pulse was automatically adjusted to minimise the residual water signal. A flip angle of greater than 90° was used to allow for T1 relaxation between the last CHESS RF pulse and the beginning of the localisation sequence.

### 2.7.2 Magnetic resonance spectroscopy data analysis

Differences in proportions of white and grey matter in the 1H-MRS voxels may confound group differences in metabolite concentrations. Thus to ensure that differences in tissue composition of the MRS voxels did not account for metabolic differences between subject groups, the 3D inversion recovery prepared spoiled GRASS dataset was segmented using statistical parametric mapping software (SPM; http://spm.ion.ucl.ac.uk) to determine the percentage of grey matter, white matter and CSF within the MRS voxel. The position of the 1H-MRS voxels relative to the 3D dataset was determined automatically using in-house software.

1H-MRS spectra were processed using LC-model on a Sun SPARC-10 workstation (Sun Microsystems Inc., Mountain View, CA). LC-model uses a linear combination of model spectra of metabolite solutions in vitro to analyse the major resonances of in vivo spectra. In this case, a basis set of alanine, aspartate, creatine, gamma-aminobutyric acid (GABA), glutamine, glutamate, glycerophosphocholine, mI, lactate, NAA, N-acetyl-aspartylglutamate (NAAg), scyllo-inositol, and taurine,

together with a baseline function were used for analysis. In addition, analysis was corrected for the CSF component of the MRS voxel. As expected, many of the metabolite peaks included in the LC-model did not reach statistical significance when fitted. However, those for NAA, mI, Cr+PCr and Cho did reach statistical significance for all spectra derived from the hippocampi and concentrations were therefore derived from these metabolite peaks.

## 2.8 Statistical analysis

In order to control for the relationship of brain volume and head size, hippocampal volumes were expressed as raw (uncorrected) volumes and when normalised, as a percentage of traced total cranial volume (TCV). Statistical analyses were carried out on both raw and corrected brain volumes. TCV is determined during childhood by the volume of brain, meninges, and cerebrospinal fluid contained within it. The normalisation to TCV provided the proportion of past hippocampal brain size.

For both MRI and 1H-MRS analyses, volumes and metabolite concentrations were normally distributed. The variables were therefore analysed using univariate analysis.

For MRI analysis, age was significantly different between groups (F 157.556, $p<0.001$), as was the gender distribution. Age, gender and TCV were added as covariates in the analysis.

For 1H-MRS analysis, between group comparisons of potential covariates including age, education and voxel of interest proportion of grey and white matter were made using univariate general linear models (GLM) with follow-up least squares difference (LSD) testing. As expected, age was significantly different between groups (F 182.84, $p<0.001$). The voxel of interest proportions of grey matter (F 6.977, $p <0.001$), white matter (F 5.678, $p <0.001$) and CSF (F 6.831, $p<0.001$) were also all significantly different. Therefore age, gender and a composite index of grey and white matter proportions of the MRS voxel [VOI proportions of grey matter/(VOI proportions of grey matter + VOI proportions of white matter)] were added as covariates in 1H-MRS analyses. Analysis was corrected for the CSF component of the MRS voxel.

Follow-up pairwise comparisons among estimated marginal means adjusting for covariates were conducted where appropriate. All significance tests used a p value of 0.05 for significance. Adjustments were made for multiple testing using the bonferroni adjustment when appropriate which allows the p value to remain at 0.05 for all significance decisions.

## 2.9 Participants

A total of 192 adults with successful MRI brain scans were included in the MRI phase of the study: 64 individuals with Down's syndrome (DS) [19 subjects with Down's syndrome who had dementia (DS+) and 45 subjects with Down's syndrome without dementia (DS-)], and 128 adults without DS [43 younger healthy control (HC)

subjects age-appropriate to the DS sample and 46 older people with Alzheimer's disease (AD), together with 39 HC subjects age-appropriate to the AD sample].

A total of 156 adults were included in the automated cortical volume and thickness study: 44 individuals with DS (14 with DS+ and 30 with DS-) and 112 older adults without DS (40 younger HC subjects age-appropriate to the DS sample; and 35 older people with AD, together with 37 HC subjects age-appropriate to the AD sample).

A total of 148 adults with successful 1H-MRS were included in the 1H-MRS phase of the study: 39 individuals with DS (19 with DS+ and 20 with DS-) and 109 older adults without DS (24 younger HC subjects age-appropriate to the DS sample; and 46 people with AD, together with 39 HC subjects age-appropriate to the AD sample).

Individuals with genetically confirmed DS were recruited from community centres, residential homes and speciality clinics in London, Birmingham, Plymouth and Newcastle upon Tyne in the United Kingdom. DS status was assessed in all participants by karyotyping. Cognitive status was measured using the Cambridge Cognitive Examination (CAMCOG). The CAMCOG is part of the Cambridge Examination of Mental Disorders of the Elderly (CAMDEX; Roth *et al.*, 1988), which apart from the CAMCOG, consists of a structured interview with the patient and an informant, together with a physical examination.

The CAMCOG is one of the diagnostic instruments that are widely used in clinical settings and in epidemiological research on dementia. It is a standardised instrument used to measure the extent of dementia and to assess the level of cognitive

impairment. The measure assesses orientation, language, memory, praxis, attention, abstract thinking, perception and calculation. The CAMCOG was previously validated for use in DS (Hon *et al.*, 1999) and is appropriate for assessing cognitive function in people with intellectual disability, unlike more standard tests of cognitive function such the Wechsler Adult Intelligence Scales. The CAMCOG incorporates, and is highly correlated with, the MMSE (Blessed *et al.*, 1991).

The AD samples were part of a larger, national longitudinal study based at the Institute of Psychiatry in London. Individuals from this study were diagnosed with dementia using the ICD-10 Research Diagnostic Criteria. Non-AD dementias were excluded in keeping with the criteria of the National Institute of Neurological and Communicative Disorders and Stroke [NINCDS] and the Alzheimer's Disease and Related Disorders Association [ADRDA] (McKhan *et al.*, 1984).

According to the NINCDS-ADRDA criteria, a diagnosis of probable Alzheimer's disease is supported by a progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia) and perception (agnosia); impaired activities of daily living and altered patterns of behaviour; a family history of similar disorders and laboratory results consisting of a normal lumbar puncture, a normal pattern or non-specific changes in EEG, and evidence of cerebral atrophy on CT with progressive documentation by serial observation. A diagnosis of definite Alzheimer's disease according to the NINCDS-ADRDA criteria requires the clinical criteria for probable Alzheimer's disease in addition to histopathologic evidence obtained from a biopsy or autopsy.

Age appropriate-HC were recruited from general practice lists and the local population. Absence of dementia was confirmed via screening with the CAMCOG and the MMSE.

All participants underwent standard physical, neurological and psychiatric screening, including routine clinical blood tests (e.g. renal, liver and thyroid function). In addition, all participants underwent a clinical MRI to exclude other brain disorders, including stroke or vascular dementia. Exclusion criteria included the presence of detectable physical (e.g. history of birth trauma or head injury) or psychiatric disorders (e.g. major depression or psychosis). None of the participants were taking antipsychotic or antidepressant medication at the time of the study. However, seven DS+ (37%) and 25 AD (54%) participants were taking acetylcholinesterase (AChE) inhibitors. It should be noted that there was a very high success rate in MR scanning in the DS+ and AD groups, with less than 20% drop out/non-compliance across all participants recruited with dementia.

The study was approved by the local and national ethics committees. After a complete description of the study was provided to the participant and the identified carer, written informed consent was obtained where possible. Where not possible, the participant's assent was obtained with formal consent provided by an identified carer.

# Chapter 3

# Results

## 3.1 Magnetic resonance imaging to compare subjects with Down's syndrome and those with Alzheimer's disease in the general population (Table 3.1)

### 3.1.1 Raw (uncorrected) volumes

Age, gender and total cranial volume (TCV) were added as covariates in the analysis. There was a significant main effect of group for the total hippocampal volume, left and right hippocampus, total temporal lobes, left and right temporal lobes, total lateral ventricles and the left and right lateral ventricles. There was a significant main effect of group and gender for whole brain volume (WBV) and TCV.

Follow-up pairwise comparisons revealed that the total hippocampal volume in addition to the left and right hippocampal volumes showed a significant reduction in AD and DS+ compared to their healthy control groups. The total hippocampal volume and the right hippocampal volume also had a significant reduction in DS+ compared to non-demented subjects with DS-. Figure 3.1 shows the hippocampal volumes for the Alzheimer's disease (AD), Alzheimer's disease healthy controls (AD HC),

demented subjects with Down's syndrome (DS+), non-demented subjects with Down's syndrome (DS-) and Down's syndrome healthy control (DS HC) groups.

The total temporal lobe volume in addition to the left and right temporal lobe volumes had a significant reduction in AD compared to its healthy control group. Figure 3.2 shows the temporal lobe volumes for the AD, AD HC, DS+, DS- and DS HC groups.

The total lateral ventricles in addition to the left and right lateral ventricles had a significant increase in AD compared to its healthy control group. The right lateral ventricle also had a significant increase in DS+ compared to its healthy control group. Figure 3.3 shows the lateral ventricle volumes for the AD, AD HC, DS+, DS- and DS HC groups.

Between DS+ and DS- and between AD and its healthy control group, there was a significant reduction in the volume of the hippocampus and temporal lobe; and a significant increase in the lateral ventricle volume.

Whole brain volume and total cranial volume had a significant reduction in DS+ and DS- compared to its healthy control group. Figure 3.4 shows the whole brain volume and Figure 3.5 shows the total cranial volume, for the AD, AD HC, DS+, DS- and DS HC groups.

Within DS individuals, the reduction in the volume of the hippocampus between DS+ and DS- was similar to that within AD cases and controls from the general population (respectively 19% and 17%). In contrast, within DS individuals, the reduction in the

volume of the temporal lobe between DS+ and DS- was almost twice that within AD cases and controls from the general population (respectively 14% and 8%). Within DS individuals, the increase in volume of the lateral ventricles between DS+ and DS- was less than that within AD cases and controls from the general population (respectively 36% and 43%).

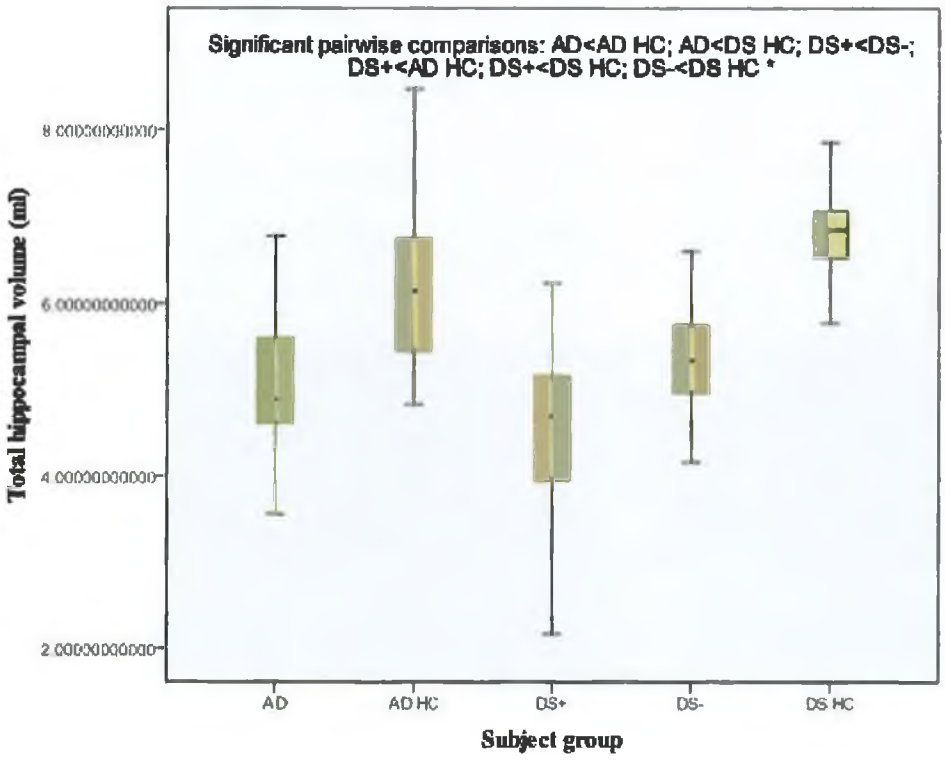


*Figure 3.1: Total hippocampal volume*

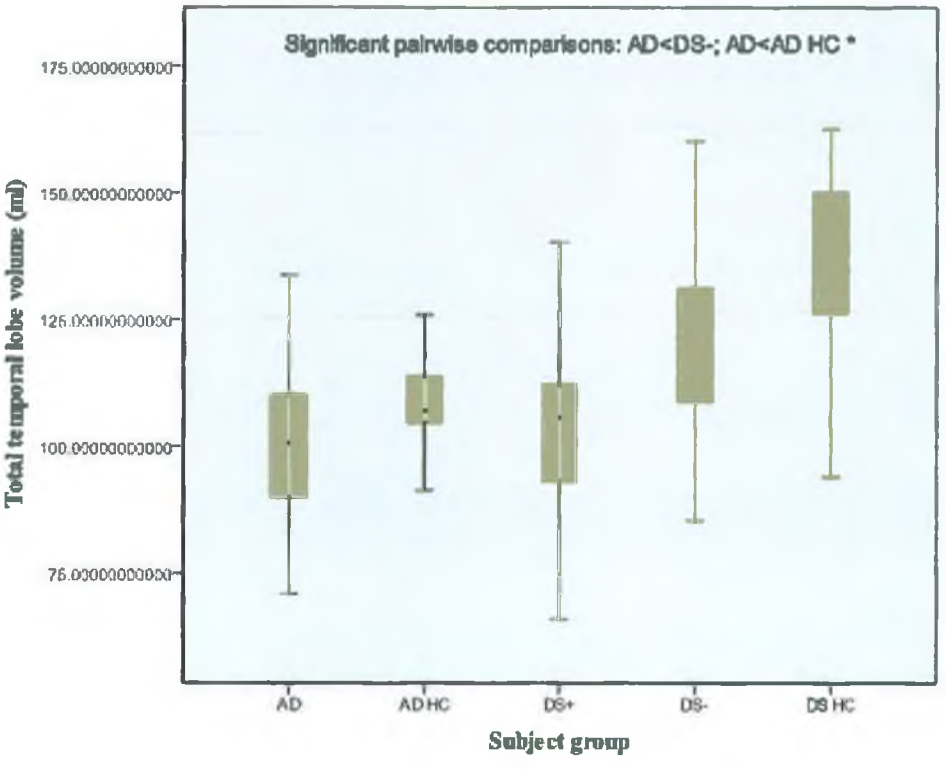


*Figure 3.2: Total temporal lobe volume*

* p <0.001; Error bars represent SD

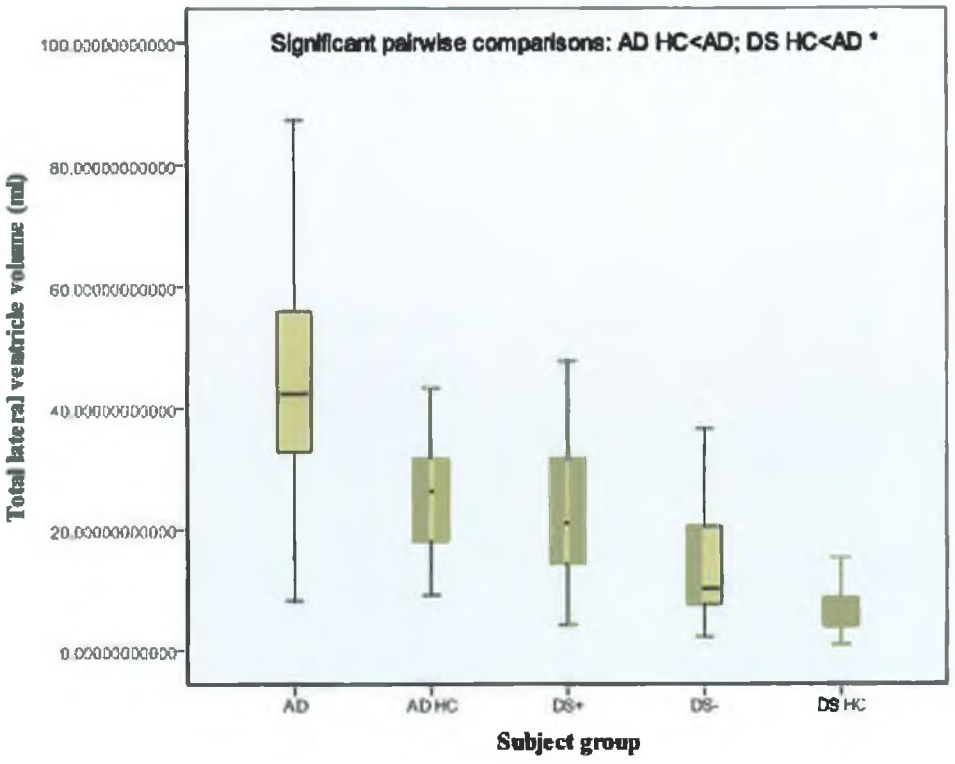


*Figure 3.3: Total lateral ventricle volume*

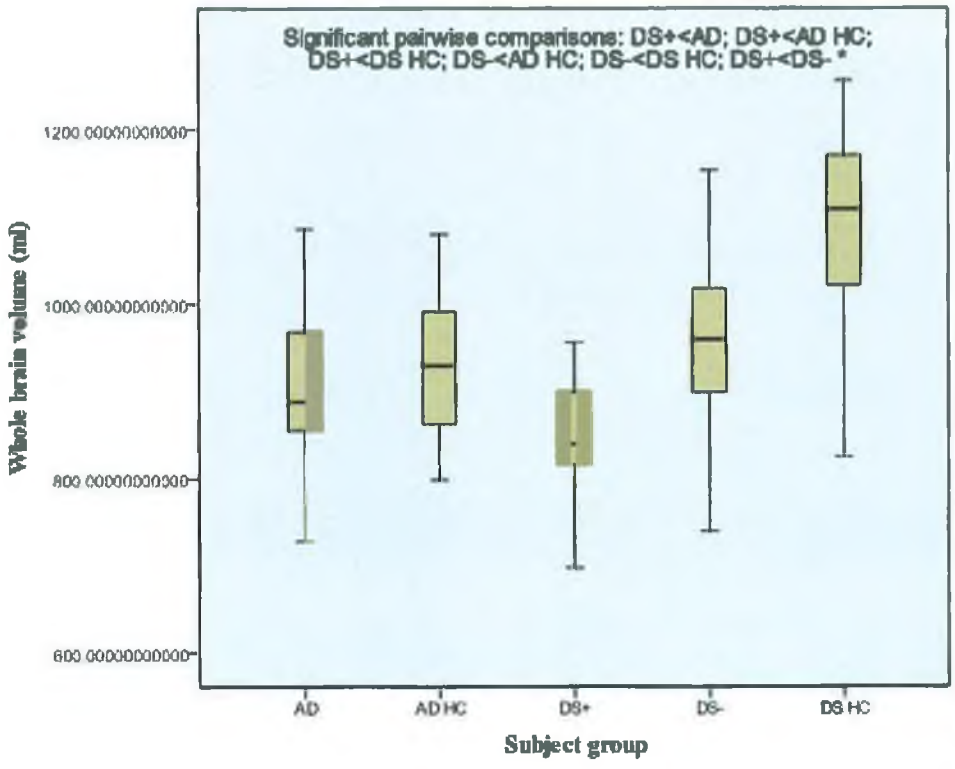


*Figure 3.4: Whole brain volume*

* p <0.001; Error bars represent SD

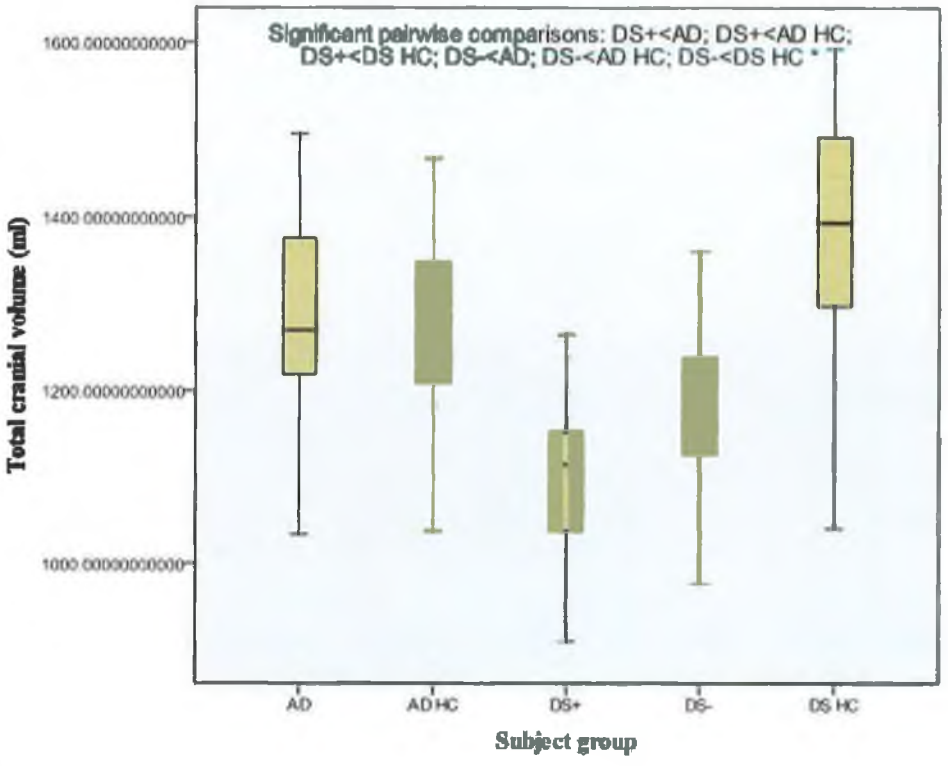


*Figure 3.5: Total cranial volume*

* p <0.001; Error bars represent SD

### 3.1.2 Volumes corrected for total cranial volume

Age, gender and TCV were added as covariates in the analysis. There was a significant main effect of group for the hippocampus, temporal lobes and the lateral ventricles. There was a significant main effect of gender for the temporal lobe.

Follow-up pairwise comparisons revealed that AD and DS+ were significantly reduced compared to their respective healthy control groups and that DS+ was significantly reduced compared to DS- for the total hippocampus, right hippocampus and left hippocampus. Figure 3.6 shows the corrected hippocampal volumes for the AD, AD HC, DS+, DS- and DS HC groups.

AD was significantly reduced compared to its healthy control group for the total temporal lobe, right temporal lobe and left temporal lobe. Figure 3.7 shows the corrected temporal lobe volumes for the AD, AD HC, DS+, DS- and DS HC groups.

AD was significantly increased compared to its healthy control group for the total lateral ventricle, right lateral ventricle and left lateral ventricle. The right lateral ventricle also had a significant increase of DS+ compared to its healthy control group. Figure 3.8 shows the corrected total lateral ventricle volumes for the AD, AD HC, DS+, DS- and DS HC groups.

Between DS+ and DS- and between AD and AD HC, there was a significant reduction in hippocampal volume and temporal lobe; and a significant increase in lateral ventricle volume.

Within DS individuals, the reduction in the volume of the hippocampus between DS+ and DS- was less than half that within AD cases and controls from the general population (respectively 7% and 15%). Similarly, the reduction in the volume of the temporal lobe between DS+ and DS- was also less than half that within AD cases and controls from the general population (respectively 2% and 5%). The increase in volume of the lateral ventricles between DS+ and DS- was similar to that between AD and AD HC (respectively 41% and 40%).

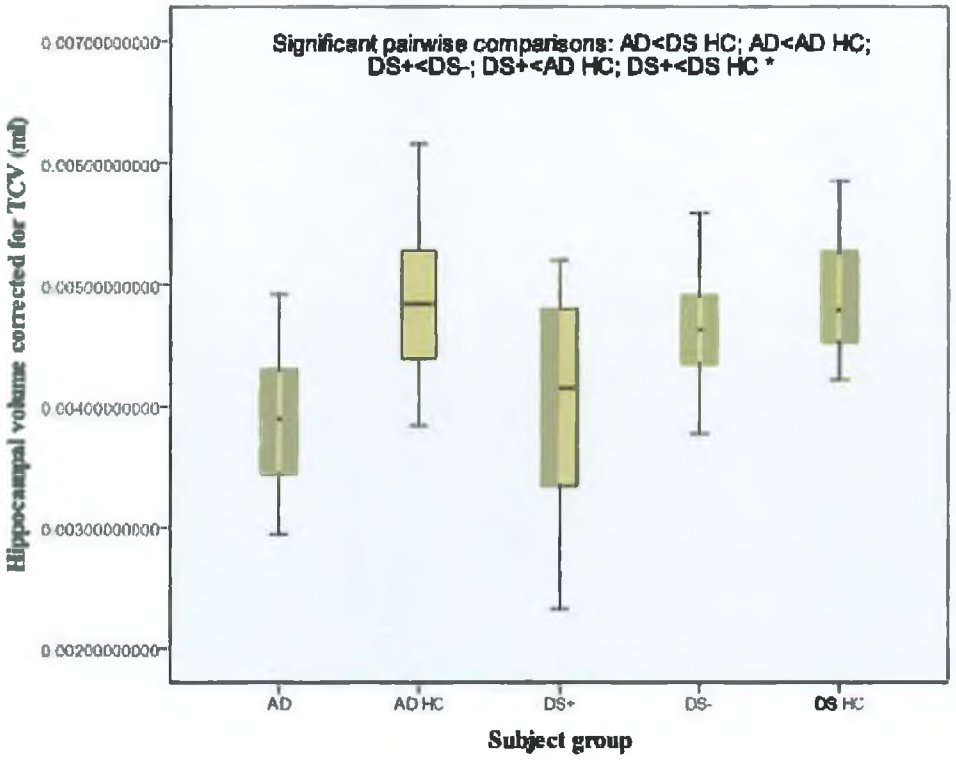


*Figure 3.6: Hippocampal volume corrected for TCV*

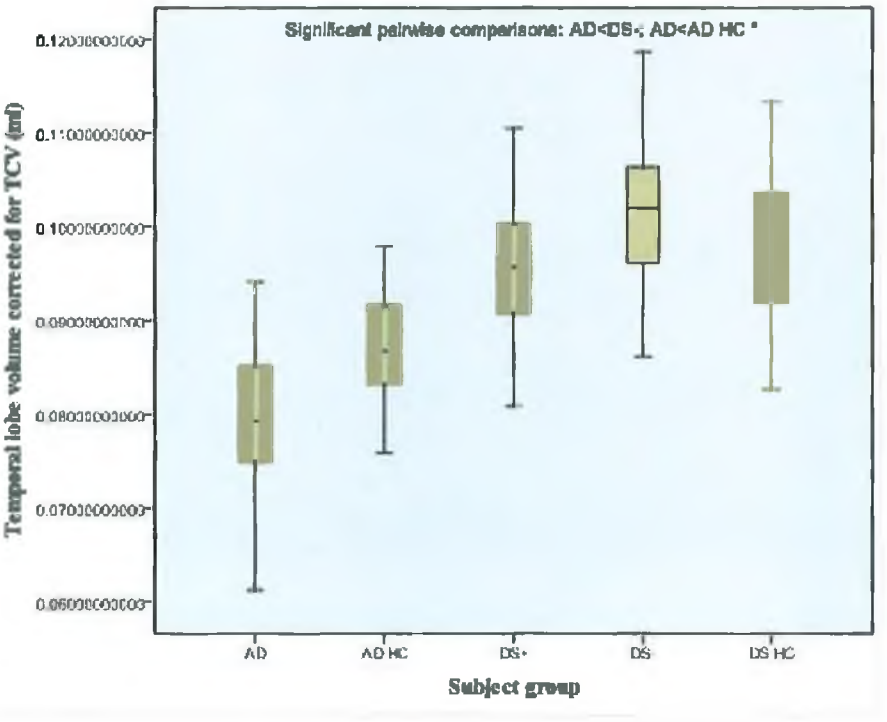


*Figure 3.7: Temporal lobe volume corrected for TCV*

* p <0.001; Error bars represent SD

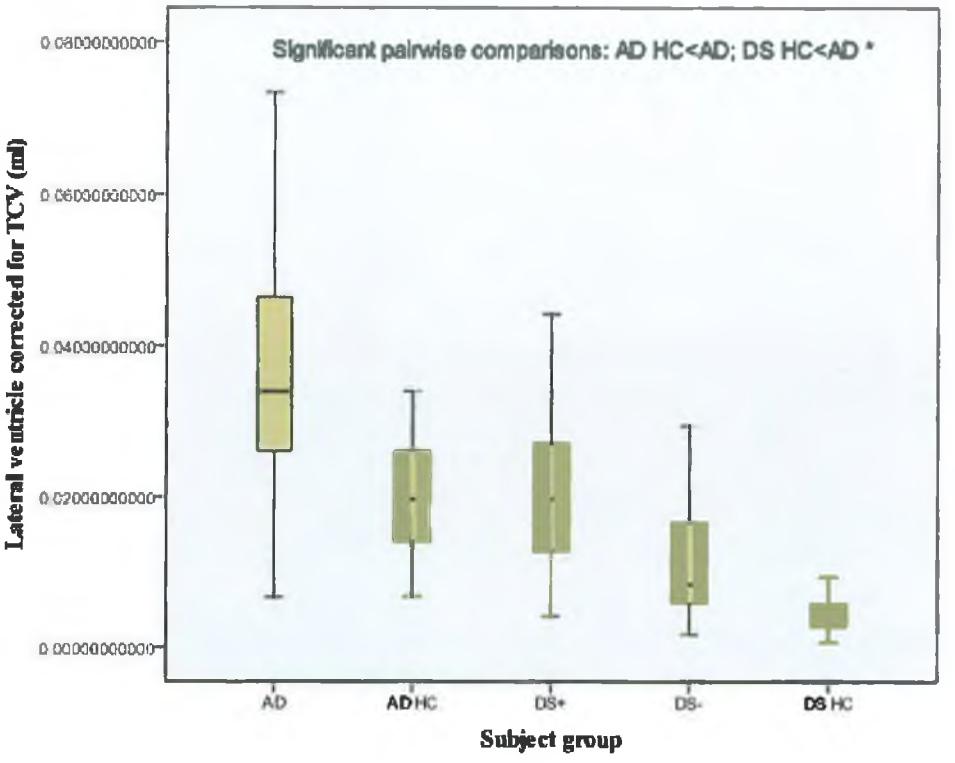


*Figure 3.8: Lateral ventricle volume corrected for TCV*

* p <0.001; Error bars represent SD

### 3.1.3 Relationship of cognitive ability to brain anatomy

In the Alzheimer's population, there was a positive correlation between MMSE and the corrected hippocampal volume (r 0.311, p 0.01) and between MMSE and the corrected temporal lobe volume (r 0.316, p 0.05). There was a negative correlation between MMSE and the corrected lateral ventricle volume (r - 0.475, p 0.01).

The Down's syndrome population showed a positive correlation between CAMCOG and the corrected hippocampal volume (r 0.216, p 0.05) and between CAMCOG and the corrected temporal lobe volume (r 0.435, p 0.01). There was a negative correlation between MMSE and the corrected lateral ventricle volume (r - 0.462, p 0.01).

| | DS+ (N=19) Mean ± SD | DS- (N=45) Mean ± SD | DS HC (N=43) Mean ± SD | AD (N=46) Mean ± SD | AD HC (N=39) Mean ± SD | F effect of group (p value) | F effect of gender (p value) | Significant pairwise comparisons |
|---|---|---|---|---|---|---|---|---|
| Age (years)* | 51.52±7.89 | 38.07±12.24 | 33.75±11.37 | 76.59±5.3 | 75.87±5.53 | 157.556 (<0.001) | NS | DS+<AD; DS+<AD HC; DS-<AD; DS-<DS+; DS HC<AD; DS HC<DS+; DS HC<AD HC |
| Education (years) | | | | 11.13±3.22 | 11.49±3 | NS | NS | NS |
| Sex (F:M) | 10:9 | 31:14 | 29:14 | 22:24 | 11:28 | | | |
| MMSE* | 9.32±4.46 | 13.88±5.56 | 15.23±2.53 | 22.48±3.74 | 28.74±3.23 | 35.757 (<0.001) | NS | AD<AD HC; DS+<AD; DS+<AD HC; DS-<AD; DS-<AD HC; DS HC<AD; DS HC<AD HC |
| CAMCOG* | 33.72±19.77 | 52.98±21.48 | 114.83±16.52 | | | 59.323 (<0.001) | NS | DS+<DS HC; DS-<DS HC |
| Whole brain volume (WBV, ml)* | 836.33±98.72 | 961.96±111.16 | 1.1±101.23 | 904.32±83.3 | 930.77±77.41 | 23.296 (<0.001) | 28.717 (<0.001) | DS+<AD; DS+<AD HC; DS+<DS HC; DS-<AD HC; DS-<DS HC; DS+<DS- |
| Total cranial volume (TCV, ml)* | 1096.46±97.76 | 1195.7±120.08 | 1387.95±125.08 | 1292.39±109.27 | 1277.27±97.95 | 38.112 (<0.001) | 55.296 (<0.001) | DS+<AD; DS+<AD HC; DS+<DS HC; DS-<AD; DS-<AD HC; DS-<DS HC |
| Hippocampus (ml)* | 4.52±1.06 | 5.56±0.81 | 6.82±0.62 | 5.13±1.04 | 6.19±0.85 | 13.242 | NS | AD<AD HC; |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | (<0.001) | | AD<DS HC; DS+<DS-; DS+<AD HC; DS+<DS HC; DS-<DS HC |
| Hippocampal volume normalised by TCV (%TCV)* | 0.41±0.09 | 0.47±0.07 | 0.49±0.05 | 0.4±0.07 | 0.5±0.06 | 13.095 (<0..001) | NS | AD<DS HC; AD<AD HC; DS+<DS-; DS+<AD HC; DS+<DS HC |
| Left hippocampus (ml)* | 2.37±0.58 | 2.97±0.59 | 3.52±0.38 | 2.62±0.51 | 3.17±0.46 | 12.723 (<0.001) | NS | AD<AD HC; AD<DS HC; DS+<DS HC; DS-<DS HC |
| Left hippocampus normalised by TCV (%TCV)* | 0.22±0.05 | 0.24±0.03 | 0.25±0.03 | 0.2±0.03 | 0.25±0.03 | 12.339 (<0.001) | NS | AD<DS-; AD<AD HC; AD<DS HC; DS+<DS HC; DS+<DS- |
| Right hippocampus (ml)* * | 2.16±0.52 | 2.7±0.47 | 3.31±0.31 | 2.48±0.0.58 | 3.02±0.44 | 11.540 (<0.001) | NS | AD<AD HC; AD<DS HC; DS+<DS HC; DS+<AD HC; DS+<DS- |
| Right hippocampus normalised by TCV (%TCV)* | 0.2±0.04 | 0.23±0.04 | 0.24±0.03 | 0.19±0.04 | 0.24±0.03 | 11.660 (<0.001) | NS | AD<AD HC; AD<DS HC; DS+<AD HC; DS+<DS HC; DS+<DS- |
| Temporal lobes (ml)* | 104.23±16.84 | 121.75±14.95 | 136.16±16.65 | 101.78±15 | 110.57±14.21 | 5.947 (<0.001) | NS | AD<DS-; AD<AD HC |
| Temporal lobes normalised by TCV (%TCV)* | 9.48±1.1 | 10.2±0.93 | 9.8±0.77 | 7.86±0.81 | 8.65±7.8 | 5.998 (<0.001) | 4.2 (0.042) | AD<DS-; AD<AD HC |
| Left temporal lobe | 52.05±8.55 | 61.26±7.68 | 68.72±8.15 | 51.97±8.35 | 56.74±9.61 | 4.967 | NS | AD<AD HC; AD<DS- |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| (ml)* | | | | | | (0.001) | | |
| Left temporal lobe normalised by TCV (%TCV)* * | 4.73±5.74 | 5.12±4.78 | 4.95±0.4 | 4.02±0.51 | 4.43±0.58 | 4.851 (0.001) | NS | AD<AD HC; AD<DS- |
| Right temporal lobe (ml)* * | 52.17±8.7 | 60.02±7.81 | 67.37±9.63 | 49.8±9.14 | 53.82±7.21 | 3.067 (0.018) | NS | AD<AD HC |
| Right temporal lobe normalised by TCV (%TCV)* * | 4.74±5.39 | 5±5.66 | 4.85±0.49 | 3.84±5.7 | 4.22±0.51 | 3.112 (0.017) | NS | AD<AD HC |
| Lateral ventricles (ml)* | 26.78±21.32 | 17.21±15.94 | 10.56±8.38 | 49±21.81 | 27.72±12.27 | 9.238 (<0.001) | NS | AD>AD HC; AD>DS HC |
| Lateral ventricles normalised by TCV (%TCV)* | 2.44±1.86 | 2.23±1.68 | 0.76±0.61 | 3.8±1.65 | 2.16±0.89 | 9.009 (<0.001) | NS | AD>AD HC; AD>DS HC |
| Left lateral ventricle (ml)* | 12.7±12.07 | 7.52±6.47 | 5.26±4.36 | 22.68±10.75 | 13.6±6.07 | 7.115 (<0.001) | NS | AD>AD HC; AD>DS HC |
| Left lateral ventricle normalised by TCV (%TCV)* | 1.16±1.04 | 0.63±0.51 | 0.38±0.32 | 1.76±0.82 | 1.06±0.45 | 6.967 (<0.001) | NS | AD>AD HC; AD>DS HC |
| Right lateral ventricle (ml)* * | 14±9.69 | 9.66±9.58 | 5.3±4.36 | 26.17±11.63 | 14.11±6.7 | 10.3 (<0.001) | NS | AD>AD HC; AD>DS HC; DS+>DS HC |
| Right lateral ventricle normalised by TCV (%TCV)* * | 1.27±0.86 | 0.8±0.7 | 0.38±0.31 | 2±0.88 | 1.1±0.48 | 9.995 (<0.001) | NS | AD>AD HC; AD>DS HC; DS+>DS HC |

* p <0.001;  * *p<0.05

***Table 3.1: Magnetic resonance imaging to compare subjects with Down's syndrome and those with Alzheimer's disease in the general population***

## 3.2 Automated volume and thickness measurements

### 3.2.1 Raw (uncorrected) volumes (Table 3.2)

There was a significant main effect of group for the left hippocampus and a significant main effect of both group and gender for right hippocampus. Follow-up comparisons revealed that both DS+ and AD had a significant reduction in left and right hippocampal volume as compared to their respective non-demented control groups. Within DS individuals, the reduction in volume of the left and right hippocampus between DS+ and DS- (both -17%) was similar to that within AD cases and controls from the general population (respectively -19% and -16%).

There was a significant main effect of group and gender for the left and right amygdala. Follow-up comparisons revealed that both DS+ and AD had a significant reduction in both left and right amygdala volume as compared to their respective non-demented control groups. Within DS individuals, the reduction of the left and right amygdala between DS+ and DS- (respectively -24% and -29%) was less than that within AD cases and controls from the general population (respectively -18% and -19%).

There was a significant effect of group and gender for both the left and right thalamus. Follow-up comparisons revealed that DS+ had a significant reduction in both left and right thalamus volume as compared to its respective non-demented control group. The percentage reduction in left and right thalamus was greater for AD cases and controls

from the general population (both -7%) compared to that between DS+ and DS- (respectively -14% and -13%).

There was no significant main effect of group or gender for either the left or right caudate. Follow-up comparisons did not reveal any significant findings.

There was a significant main effect of group and gender for both the left and right pallidum. Follow-up comparisons did not reveal any significant findings for DS+ or AD as compared to their respective non-demented control groups.

There were significant main effects of group and gender for both the left and right putamen. Follow-up comparisons did not produce any significant findings.

There was a significant main effect of group and gender for the optic chiasm. Follow-up comparisons revealed that AD had a significant increase in the optic chiasm volume compared to its non-demented control group. AD experienced a +11% volume increase in optic chiasm compared to its control group, while DS+ had a -6% volume reduction compared to DS-.

There was a significant main effect of group and gender for the brain stem. Follow-up comparisons revealed that DS+ had a significant reduction in brain stem volume when compared to its non-demented control group. DS+ experienced a -8% volume reduction in brain stem compared to DS-, while AD had a +2% volume increase compared to its control group.

There was a significant main effect of group and gender for both the left and right cerebellar cortex. Follow-up comparisons revealed that DS+ had a significant reduction in both left and right cerebellar cortex volume when compared to its non-demented control group. The percentage reduction in left and right cerebellar cortex volume was greater for DS+ compared to DS- (respectively -14% and -11%) than the reduction between AD and its control group (respectively -0.5% and -0.4%).

There was a significant main effect of group for both the left and right cerebellar white matter. Follow-up comparisons revealed that DS+ had a significant reduction in both left and right cerebellar white matter when compared to its non-demented control groups. DS+ experienced a greater volume reduction compared to DS- for both left and right cerebellar white matter (respectively -10% and -5%). While AD experienced a greater volume increase compared to its control group (respectively +10% and +1%).

There was a significant main effect of group and gender for both the left and right cerebral white matter. Follow-up comparisons revealed that DS+ had a significant reduction in left and right cerebral white matter compared to its non-demented control group. The reductions in the left and right cerebral white matter for DS+ compared to DS- were -5% and -25% respectively; while the reductions of AD compared to its control group were -6% and -0.1% respectively.

There was a significant main effect of group and gender for both the left and right cerebral cortex. Follow-up comparisons revealed that DS+ and AD had a significant reduction in left and right cerebral cortex compared to their respective non-demented

control groups. The reductions in the left and right cerebral cortex volumes for DS+ compared to DS- (respectively -14% and -13%) were greater that of AD compared to its healthy control group (both -7%).

There was a significant main effect of group for the left accumbens area and of both group and gender for the right accumbens area. Follow-up comparisons revealed that DS+ had a significant reduction in left accumbens area compared to its non-demented control group and that both DS+ and AD had a significant reduction in the right accumbens area compared to their comparison control groups. The reduction in the left and right accumbens volume was greater for DS+ compared to DS- (respectively -14% and -16%) than for AD compared to its control group (-6% and -9%).

There was a significant main effect of group and gender for both the left and right ventral dorsal columns. Follow-up comparisons revealed that DS+ and had a significant reduction in the left and right ventral dorsal columns compared to its non-demented control group. The reduction in the volume of the left and right ventral dorsal columns was -0.3% and -12% respectively when DS+ was compared to DS-. When AD was compared to its control group, there was a -12% reduction in volume for the left ventral dorsal column volume and a +0.3% increase for the right ventral dorsal column volume.

There was a significant main effect of group and gender for the anterior corpus callosum and the central corpus callosum. There was a significant main effect of group for the posterior and mid-posterior corpus callosum and no significant main effects for the mid-anterior corpus callosum. Follow-up comparisons revealed

significant findings for the central corpus callosum, a reduction in DS+ when compared to its non-demented control group. The anterior, central and mid-posterior corpus callosum volumes produced greater reductions when AD was compared to its control group (respectively -14%, -15% and -16%), than when DS+ was compared to DS- (respectively -7%, -8%, -0.3%). The posterior corpus callosum was reduced when AD was compared to its control group (-14%) and increased with DS+ was compared to DS- (+3%).

There was a significant main effect of group and gender for CSF. Follow-up comparisons did not produce any significant findings.

There was a significant main effect of group and gender for the third ventricle. Follow-up comparisons revealed that AD had a significant increase in third ventricle volume when compared to its non-demented control group. The increase in third ventricle volume when AD was compared to its control group (+31%) was almost double that when DS+ was compared to DS- (+16%).

There was a significant main effect of group for the fourth ventricle. Follow-up comparisons did not produce any significant findings for DS+ or AD when compared to their respective non-demented control groups.

There were no significant main effects of group or gender for the fifth ventricle. Follow-up comparisons did not produce any significant findings.

There was a significant main effect of group for both the left and right inferior lateral ventricles. Follow-up comparisons revealed a significant increase in DS+ and AD compared to their respective non-demented control groups for the left inferior lateral ventricle and for AD compared to its non-demented control group for the right inferior lateral ventricle. The increase in left and right inferior lateral ventricle volume was greater when AD was compared to its control group (both +71%) than when DS+ was compared to DS- (respectively +54% and +55%).

There was a significant main effect of group and gender for both the left and right lateral ventricles. Follow-up comparisons revealed a significant increase in AD volume of both left and right lateral ventricles compared to its non-demented control group. The increases in left and right lateral ventricles was greater for AD compared to its control group (respectively +78% and +39%) than when DS+ was compared to DS- (+28% and +32%).

There was a significant main effect of group for both the left and right vessel. Follow-up comparisons did not however produce any significant findings for DS+ or AD when compared to their respective non-demented control groups for either the left or right vessel.

There were no significant main effects of either group or gender for the non-white matter hyperdensities. Follow-up comparisons did not produce any significant findings.

There was a significant main effect of group for the white matter hyperdensities. Follow-up comparisons revealed that AD had a significant increase in white matter hyperdensities when compared to its non-demented control group. The increase in white matter hyperdensities was more than four times greater for AD compared to its control group (+48%) than when DS+ was compared to DS- (+10%).

### 3.2.2 Volumes corrected for total cranial volume (Table 3.2)

There was a significant main effect of group and gender for the normalised left and right hippocampus. Follow-up comparisons revealed a significant reduction for AD compared to its non-demented control group for the normalised left hippocampus and for both AD and DS+ compared to their respective non-demented control groups for the normalised right hippocampal volume. The volume reductions for the left and right hippocampus were greater for AD compared to its control group (respectively -20% and -22%) than for DS+ compared to DS- (respectively -15% and -4%).

There was a significant main effect of group and gender for the normalised left and right amygdala. Follow-up comparisons revealed a significant reduction for AD compared to its non-demented control group for both the normalised left and right amygdala compared to its respective non-demented control group. The volume reductions for the left and right amygdala were greater for AD compared to its control group (respectively -30% and -27%) than for DS+ compared to DS- (respectively -9% and -23%).

There was a significant main effect of group and gender for the normalised left and right thalamus. Follow-up comparisons did not produce any significant findings for AD or DS+ compared to their respective non-demented control groups for either the normalised left or right thalamus.

There was a significant main effect of group and gender for the normalised left caudate volume and a significant main effect of gender for the right caudate volume. Follow-up comparisons did not produce any significant findings for either AD or DS+ compared to their respective non-demented control groups.

There was a significant main effect of group for the normalised left and right pallidum. Follow-up comparisons did not produce any significant findings for either AD or DS+ compared to their healthy control groups.

There was a significant main effect of group and gender for the normalised left and right putamen. Follow-up comparisons for the normalised left putamen revealed a significantly reduction for AD compared to its non-demented control group but no significant findings for either AD or DS+ compared to their respective non-demented control groups for the normalised right putamen. Within DS individuals, the reduction in volume of the left and right putamen between DS+ and DS- (respectively -13% and -11%) was similar to that within AD cases and controls from the general population (both -10%).

There was a significant main effect of group for the normalised optic chiasm. Follow-up comparisons did not produce any significant findings for either AD or DS+ compared to their non-demented control groups.

There was a significant main effect of group and gender for the normalised brain stem volume. Follow-up comparisons revealed that DS+ had a significant reduction in the brain stem volume compared to its non-demented control group.

There was a significant main effect of group and gender for the normalised left and right cerebellar cortex. Follow-up comparisons revealed that both the normalised left and right cerebellar cortex had a significant reduction in DS+ compared to its non-demented control group. DS+ had a greater reduction in the left and right normalised cerebellar cortex compared to DS- (respectively -11% and -8%) than AD compared to its non-demented control group (both -5%).

There was a significant main effect of group and gender for the normalised left and right cerebellar white matter. Follow-up comparisons revealed significant reductions in DS+ compared to its non-demented control group for both the left and right normalised cerebellar white matter volumes. Within DS individuals, the reduction in volume of the left and right normalised cerebellar white matter between DS+ and DS- (respectively -6% and -3%) was similar to that within AD cases and non-demented controls from the general population (respectively -4% and -3%).

There was a significant main effect of group and gender for the normalised left and right cerebral cortex. Follow-up comparisons revealed that AD had a significant

reduction compared to its non-demented control group for both the left and right cerebral cortex. Within DS individuals, the reduction in volume of the left and right normalised cerebral cortex volumes between DS+ and DS- (both -9%) was similar to that within AD cases and controls from the general population (respectively both -11%).

There was a significant main effect of group and gender for the normalised left and right cerebral white matter. Follow-up comparisons did not reveal any significant findings for either AD or DS+ compared to their non-demented control groups for either the left or right normalised cerebral white matter.

There was a significant main effect of both group and gender for the normalised left and right accumbens area. Follow-up comparisons revealed a significant reduction in AD compared to its non-demented control group for the normalised right accumbens area and no significant findings for the normalised left accumbens area.

There was a significant main effect of group and gender for the normalised left and right ventral dorsal columns. Follow-up comparisons did not produce any significant findings for either AD or DS+ compared to their respective non-demented control groups for either the left or right normalised ventral dorsal columns. The reduction in the left and right normalised ventral dorsal columns was greater for DS+ compared to DS- (respectively -10% and -7%) than within AD group compared to its non-demented controls (both -4%).

There was a significant main effect of group and gender for the normalised anterior, mid-anterior, central, posterior and mid-posterior corpus callosum. Follow-up comparisons revealed that there was a significant increase in DS+ compared to its non-demented control group for the normalised anterior and posterior corpus callosum. The normalised anterior, mid-anterior, central, posterior and mid-posterior corpus callosum volumes were reduced in AD compared to its non-demented control group (respectively – 25%, -20%, -15%, -18% and -15%). DS+ compared to DS- showed a reduction in the normalised anterior and central corpus callosum (respectively -2% and -4%) and an increase in the normalised mid-anterior, posterior and mid-posterior corpus callosum (respectively +1%, +7% and +4%).

There was a significant main effect of group and gender for the normalised CSF. Follow-up comparisons revealed a significant increase in DS+ compared to its non-demented control group. The increase in the normalised CSF volume was greater for AD compared to its non-demented controls (+9%) than for DS+ compared to DS- (+5%).

There was a significant main effect of group and gender for the normalised third ventricle volume. Follow-up comparisons revealed a significant increase in AD and DS+ compared to their respective non-demented control groups. The increase in the normalised third ventricle volume for AD compared to its non-demented controls was more than twice that for DS+ compared to DS- (respectively +23% and -11%).

There was a significant main effect of group for the normalised fourth ventricle volume. Follow-up comparisons did not produce any significant findings for AD or DS+ compared to their non-demented control groups.

There was no significant main effect of group or gender for the normalised fifth ventricle volume. Follow-up comparisons did not produce any significant findings.

There was a significant main effect of gender for the normalised left and right inferior lateral ventricle volumes. Follow-up comparisons revealed a significant increase in both AD and DS+ compared to their respective non-demented control groups for both the left and right normalised inferior lateral ventricle volumes. The increase in the left and right normalised inferior lateral ventricle was greater for AD compared to its non-demented control group (respectively +67% and +63%) than for DS+ compared to DS- (respectively +50% and +57%).

There was a significant main effect of group and gender for the normalised left and right lateral ventricle volumes. Follow-up comparisons revealed significant increases in AD and DS+ compared to their respective non-demented control groups for both the left and right normalised lateral ventricle volumes. The increase in normalised left and right lateral ventricle was +41% and +36% respectively for AD compared to its non-demented control group and +31% and +35% for DS+ compared to DS-.

There was a significant main effect of group for the normalised left and right vessel volumes. Follow-up comparisons did not produce any significant findings for AD or

DS+ compared to their non-demented control groups for either the left or right normalised vessel volumes.

There were no significant main effects of group or gender for the normalised non-white matter hyperdensities. Follow-up comparisons did not produce any significant findings.

There was a significant main effect of group for the normalised white matter hyperdensities. Follow-up comparisons revealed a significant increase in AD compared to its non-demented control group. The increase in normalised white matter hyperdensities was more than three times greater for AD compared to its non-demented control group than for DS+ compared to DS- (respectively +45% and +13%).

| | DS+ (N=14) Mean ± SD | DS- (N=30) Mean ± SD | DS HC (N=40) Mean ± SD | AD (N=35) Mean ± SD | AD HC (N=37) Mean ± SD | F effect of group (p value) | F effect of gender (p value) | Significant pairwise comparisons |
|---|---|---|---|---|---|---|---|---|
| Age (years)* | 50.61±8.62 | 38.88±12.61 | 34.07±11.64 | 75.77±5.5 | 76.14±5.43 | 138.455 (<0.001) | NS | DS+<AD; DS HC<AD HC; DS-<AD; DS-<AD HC; DS-<DS+; DS HC<AD; DS HC<DS+ |
| Education (years)* | | | | 11.46±3.38 | 11.71±3.01 | NS | NS | NS |
| Sex (F:M) | 7:7 | 8:22 | 14:26 | 18:17 | 28:9 | | | |
| MMSE* | 9.29±4.81 | 14.67±5.08 | 15.15±2.66 | 23.23±3.54 | 28.51±3.81 | 34.479 (<0.001) | NS | AD<AD HC; DS+<AD; DS+<AD HC; DS+<DS-; DS+<DS HC; DS-<AD; DS-<AD HC; DS-<AD HC; DS HC<AD HC |
| CAMCOG* | 36.54±21.4 | 54.81±21.04 | 114.63±17.41 | | | 77.423 (<0.001) | NS | DS+<DS HC; DS-<DS HC |
| Total cranial volume (TCV)* | 1373.43±152.87 | 1440.77±182.99 | 1702.98±187.02 | 1624.28±185 | 1542.79±141.05 | 18.317 (<0.001) | 46.687 (<0.001) | DS+<AD; DS+<AD HC; DS+<DS HC; DS-<AD; DS-<AD HC; DS-<DS HC |
| Left hippocampus* | 3.14±0.53 | 3.86±0.39 | 4.56±0.42 | 3.21±0.55 | 3.89±0.39 | 30.522 (<0.001) | NS | AD<AD HC; AD<DS HC; DS+<DS-; DS+<AD HC; DS+<DS HC; DS-<AD HC; DS-<DS HC |
| Left hippocampus normalised by TCV (%TCV)* | 0.23±0.04 | 0.27±0.03 | 0.27±0.02 | 0.2±0.03 | 0.25±0.03 | 17.528 (<0.001) | 19.859 (<0.001) | AD<DS-; AD<AD HC; AD<DS HC; DS+<DS-; DS+<AD HC |
| Right hippocampus* | 3.4±0.56 | 4.03±0.41 | 4.82±0.42 | 3.46±0.51 | 4.15±0.41 | 33.746 (<0.001) | 4.999 (0.027) | AD<AD HC; AD<DS HC; DS+<DS-; DS+<AD HC; DS+<DS HC; DS-<AD HC; DS-<DS HC |
| Right hippocampus normalised by TCV (% TCV)* | 0.25±0.04 | 0.29±0.03 | 0.29±0.03 | 0.21±0.03 | 0.27±0.02 | 17.170 (<0.001) | 18.743 (<0.001) | AD<DS-; AD<AD HC; AD<DS HC; DS+<DS-; DS+<AD HC; DS+<DS HC |
| Left amygdala* | 1.36±0.24 | 1.65±0.22 | 1.8±0.2 | 1.2±0.29 | 1.58±0.23 | 18.364 | 4.971 | AD<AD HC; AD<DS HC; |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | (<0.001) | (0.027) | DS+<AD HC; DS+<DS HC |
| Left amygdala normalised by TCV (% TCV)** | 0.1±0.02 | 0.11±0.02 | 0.11±0.01 | 0.07±0.02 | 0.1±0.01 | 18.396 (<0.001) | 6.128 (0.014) | AD<DS+; AD<DS-; AD<AD HC; AD<DS HC; DS+<DS- |
| Right amygdala* | 1.45±0.26 | 1.8±0.2 | 1.87±0.18 | 1.32±0.29 | 1.87±0.18 | 18.309 (<0.001) | 6.163 (0.014) | AD<DS-; AD<AD HC; AD<DS HC; DS+<DS-; DS+<AD HC; DS+<DS HC |
| Right amygdala normalised by TCV (% TCV)* | 0.1±0.02 | 0.13±0.02 | 0.11±0.01 | 0.08±0.01 | 0.11±0.01 | 28.266 (<0.001) | 8.876 (0.003) | AD<DS+; AD<DS-; AD<AD HC; AD<DS HC; DS+<DS-; DS HC<DS- |
| Left thalamus* | 5.27±0.65 | 6.1±0.79 | 7.11±0.76 | 5.47±0.54 | 5.59±0.51 | 14.873 (<0.001) | 4.544 (0.035) | DS+<AD; DS+<AD HC; DS+<DS HC; DS-<DS HC |
| Left thalamus normalised by TCV (% TCV)** | 0.39±0.04 | 0.43±0.04 | 0.42±0.04 | 0.34±0.04 | 0.36±0.03 | 3.790 (0.006) | 28.280 (<0.001) | AD<DS-; DS+<DS- |
| Right thalamus* | 5.2±0.68 | 5.96±0.77 | 6.98±0.77 | 5.39±0.5 | 5.49±0.5 | 15.275 (<0.001) | 4.553 (0.035) | DS+<AD; DS+<AD HC; DS+<DS HC; DS-<DS HC |
| Right thalamus normalised by TCV (% TCV)* | 0.38±0.05 | 0.04±0.05 | 0.41±0.04 | 0.33±0.03 | 0.36±0.03 | 2.457 (0.048) | 29.456 (<0.001) | NS |
| Left caudate | 2.98±0.47 | 3.28±0.47 | 3.49±0.44 | 3.26±0.5 | 3.25±0.66 | NS | NS | NS |
| Left caudate normalised by TCV (% TCV)** | 0.22±0.03 | 0.23±0.03 | 0.21±0.02 | 0.2±0.03 | 0.21±0.04 | 3.798 (0.006) | 7.846 (0.006) | DS HC<DS- |
| Right caudate* | 2.98±3.35 | 3.35±0.47 | 3.35±0.71 | 3.42±0.63 | 3.35±0.71 | 2.795 (0.028) | NS | NS |
| Right caudate normalised by TCV (% TCV)* | 0.22±0.03 | 0.23±0.03 | 0.21±0.02 | 0.21±0.03 | 0.21±0.04 | NS | 11.550 (0.001) | NS |
| Left pallidum** | 1.24±0.25 | 1.41±0.24 | 1.56±0.19 | 1.28±0.2 | 1.26±0.17 | 3.782 (0.006) | 16.465 (<0.001) | DS+<AD; DS+<AD HC |
| Left pallidum normalised by TCV (% TCV) ** | 0.09±0.01 | 0.1±0.01 | 0.09±0.01 | 0.07±0.01 | 0.08±0.01 | 2.660 (0.035) | NS | DS-HC<DS- |
| Right pallidum** | 1.23±0.27 | 1.41±0.3 | 1.56±0.24 | 1.24±0.21 | 1.21±0.15 | 3.322 | 9.281 | DS+<AD; DS+<AD HC |

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| | | | | | | (0.021) | (0.003) | |
| Right pallidum normalised by TCV (% TCV)** | 0.09±0.01 | 0.1±0.01 | 0.09±0.01 | 0.08±0.01 | 0.08±0.01 | 3.496 (0.009) | NS | DS-HC<DS- |
| Left putamen* | 4.81±0.71 | 5.55±0.69 | 5.77±0.68 | 4.34±0.75 | 4.63±0.59 | 3.140 (0.016) | 5.355 (0.022) | NS |
| Left putamen normalised by TCV (% TCV)* | 0.35±0.05 | 0.4±0.06 | 0.34±0.04 | 0.27±0.05 | 0.3±0.03 | 12.146 (<0.001) | 10.235 (0.002) | AD<DS+; AD<DS-; AD<AD HC; DS HC<DS- |
| Right putamen* | 4.6±0.64 | 5.44±0.68 | 5.51±0.64 | 4.2±0.67 | 4.39±0.72 | 2.477 (0.047) | 4.560 (0.034) | NS |
| Right putamen normalised by TCV (% TCV)* | 0.34±0.04 | 0.38±0.05 | 0.33±0.04 | 0.26±0.04 | 0.29±0.04 | 13.692 (<0.001) | 12.021 (0.001) | AD<DS-; DS-HC<DS- |
| Optic chiasm** | 0.29±0.04 | 0.31±0.04 | 0.33±0.06 | 0.37±0.06 | 0.33±0.06 | 4.861 (0.001) | 5.418 (0.021) | AD HC<AD; DS+<AD |
| Optic chiasm normalised by TCV (% TCV)** | 0.0216±0.003 | 0.022±0.003 | 0.019±0.003 | 0.023±0.004 | 0.021±0.004 | 3.790 (0.006) | NS | DS HC<DS- |
| Brain stem* | 14.78±1.77 | 16.11±2 | 21.83±2.48 | 19.69±2.18 | 19.3±1.18 | 41.729 (<0.001) | 8.492 (0.004) | DS+<AD; DS+<AD HC; DS+<DS HC; DS-<AD; DS-<AD HC; DS-<DS HC |
| Brain stem normalised by TCV (% TCV)* | 1.08±0.01 | 1.11±0.13 | 1.29±0.13 | 1.12±0.15 | 1.26±0.12 | 9.075 (<0.001) | 10.633 (0.001) | DS+<AD; DS+<AD HC; DS+<DS HC; DS-<DS HC |
| Left cerebellar cortex* | 36.09±5.83 | 42.08±4.92 | 57.89±6.49 | 47.95±5.18 | 48.18±5.4 | 55.010 (<0.001) | 10.234 (0.002) | DS+<AD; DS+<AD HC; DS+<DS HC; DS-<AD; DS-<AD HC; DS-<DS HC |
| Left cerebellar cortex normalised by TCV (% TCV)* | 2.62±0.31 | 2.95±0.39 | 3.42±0.4 | 2.97±0.32 | 3.13±0.28 | 15.509 (<0.001) | 9.415 (0.003) | DS+<AD; DS+<AD-HC; DS+<DS HC; DS-<AD HC; DS-<DS HC |
| Right cerebellar cortex* | 37.29±5.75 | 41.72±5.19 | 57.95±6.75 | 48.32±5.33 | 48.51±5.74 | 46.682 (<0.001) | 5.037 (0.026) | DS+<AD; DS+<AD HC; DS+<DS HC; DS-<AD; DS-<AD HC; DS-<DS HC |
| Right cerebellar cortex normalised | 2.71±0.29 | 2.93±0.42 | 3.43±0.43 | 2.99±0.31 | 3.15±0.31 | 12.237 (<0.001) | 15.213 (<0.001) | DS+<AD; DS+<AD HC; DS+<DS HC; DS-<DS HC |

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| by TCV (% TCV) * | | | | | | | | |
| Left cerebellar white matter* | 8.99±1.19 | 10.01±1.97 | 15.8±2.11 | 14.33±2.27 | 14.26±1.79 | 46.344 (<0.001) | NS | DS+<AD; DS+<AD HC; DS+<DS HC; DS-<AD; DS-<AD HC ; DS-<DS HC |
| Left cerebellar white matter normalised by TCV (% TCV) * | 0.66±0.09 | 0.7±0.15 | 0.93±0.12 | 0.89±0.15 | 0.93±0.13 | 19.413 (<0.001) | 17.204 (<0.001) | DS+<AD; DS+<AD HC; DS+<DS HC; DS-<DS HC |
| Right cerebellar white matter* | 9.47±1.04 | 10.1±1.9 | 15.7±2.1 | 14.47±2.23 | 14.28±2.06 | 40.944 (<0.001) | NS | DS+<AD; DS+<AD HC; DS+<DS HC; DS-<AD; DS-<AD HC; DS-<DS HC |
| Right cerebellar white matter normalised by TCV (% TCV) * | 0.69±0.08 | 0.71±0.14 | 0.93±0.13 | 0.9±0.14 | 0.93±0.14 | 16.166 (<0.001) | 15.725 (<0.001) | DS+<AD; DS+<AD HC; DS+<DS HC; DS-<DS HC |
| Left cerebral cortex* | 219.83±27.75 | 254.29±26.27 | 286.96±28.55 | 217.37±21.71 | 233.63±22.26 | 17.442 (<0.001) | 14.363 (<0.001) | AD<AD HC; DS+<AD; DS+<AD HC; DS+<DS HC; DS-<DS HC |
| Left cerebral cortex normalised by TCV (% TCV) * | 16.08±1.85 | 17.75±1.49 | 16.91±1.26 | 13.48±1.43 | 15.17±0.98 | 11.885 (<0.001) | 18.725 (<0.001) | AD<DS-; AD<AD HC; DS+<DS-; DS HC<DS- |
| Right cerebral cortex* | 219.46±28.62 | 252.49±28.62 | 285.09±29.76 | 215.39±22.3 | 231.85±22.21 | 14.391 (<0.001) | 7.665 (0.006) | AD<AD HC; DS+<AD HC; DS+<DS HC; DS-<DS HC |
| Right cerebral cortex normalised by TCV (% TCV) * | 16.07±1.9 | 17.61±1.51 | 16.8±1.25 | 13.35±1.39 | 15.06±1.11 | 11.315 (<0.001) | 28.536 (<0.001) | AD<DS+; AD<DS-; AD<AD HC; DS HC<DS- |
| Left cerebral white matter* | 174.04±24.68 | 191.78±25.99 | 230.78±27.05 | 195.66±27.08 | 196.61±18.86 | 14.632 (<0.001) | 17.570 (<0.001) | DS+<AD; DS+<AD HC; DS+<DS HC; DS-<DS HC |
| Left cerebral white matter normalised by TCV (%TCV) * | 12.69±1.34 | 13.34±1.26 | 13.57±0.78 | 12.06±1.22 | 12.77±0.98 | 2.632 (0.037) | 4.168 (0.043) | NS |
| Right cerebral white matter* | 175.32±21.98 | 193.12±24.42 | 232.96±27.18 | 198.71±27.39 | 198.91±19.36 | 15.847 (<0.001) | 16.966 (<0.001) | DS+<AD; DS+<AD HC; DS+<DS HC; DS-<DS HC |
| Right cerebral | 12.81±1.34 | 13.46±1.31 | 13.7±0.84 | 12.25±1.2 | 12.92±0.96 | 3.859 | 5.311 | AD<DS-; AD<DS HC |

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| white matter normalised by TCV (% TCV) ** | | | | | | (0.005) | (0.023) | |
| Left accumbens area* | 0.45±0.1 | 0.52±0.11 | 0.67±0.11 | 0.49±0.11 | 0.52±0.11 | 11.108 (<0.001) | NS | DS+<AD HC; DS+<DS HC; DS-<DS HC |
| Left accumbens area normalised by TCV (%TCV) * | 0.03±0.008 | 0.036±0.007 | 0.04±0.007 | 0.03±0.0006 | 0.034±0.008 | 3.235 (0.014) | 17.384 (<0.001) | NS |
| Right accumbens area* | 0.46±0.06 | 0.55±0.08 | 0.63±0.1 | 0.48±0.09 | 0.53±0.1 | 11.402 (<0.001) | 26.848 (<0.001) | AD<AD HC; DS+<AD HC; DS+<DS HC; DS-<AD HC |
| Right accumbens area normalised by TCV (% TCV) * | 0.03±0.004 | 0.04±0.005 | 0.04±0.004 | 0.02±0.005 | 0.03±0.005 | 8.368 (<0.001) | NS | AD<AD HC |
| Left ventral dorsal column* | 3.6±0.4 | 4.11±0.37 | 4.63±0.49 | 3.84±0.41 | 3.85±0.39 | 12.588 (<0.001) | 13.232 (<0.001) | DS+<AD; DS+<AD HC; DS+<DS HC; DS-<DS HC |
| Left ventral dorsal column normalised by TCV (% TCV) ** | 0.26±0.02 | 0.29±0.03 | 0.27±0.02 | 0.24±0.03 | 0.25±0.02 | 4.963 (0.001) | 15.651 (<0.001) | AD<DS-; DS HC<DS- |
| Right ventral dorsal column* | 3.66±0.53 | 4.17±0.48 | 4.69±0.43 | 3.81±0.43 | 3.8±0.37 | 11.690 (<0.001) | 18.636 (<0.001) | DS+<AD; DS+<AD HC; DS+<DS HC; DS-<DS HC |
| Right ventral dorsal column normalised by TCV (% TCV) ** | 0.27±0.02 | 0.29±0.03 | 0.28±0.02 | 0.24±0.03 | 0.25±0.02 | 3.263 (0.013) | 8.175 (0.005) | DS-HC<DS- |
| Anterior corpus callosum** | 0.8±0.25 | 0.86±0.23 | 0.8±0.12 | 0.56±0.15 | 0.65±0.12 | 4.076 (0.004) | 4.078 (0.045) | AD<DS- |
| Anterior corpus callosum normalised by TCV (% TCV) * | 0.059 ±0.02 | 0.06±0.02 | 0.05±0.007 | 0.03±0.009 | 0.04±0.009 | 15.770 (<0.001) | 24.406 (<0.001) | AD<DS+; AD<DS-; AD HC<DS+; AD HC<DS-; DS HC<DS+; DS HC<DS- |
| Mid-anterior corpus callosum* | 0.4±0.17 | 0.42±0.15 | 0.42±0.08 | 0.25±0.08 | 0.32±0.07 | NS | NS | NS |
| Mid-anterior corpus callosum | 0.0297±0.01 | 0.0293±0.01 | 0.03±0.005 | 0.016±0.005 | 0.02±0.005 | 7.351 (<0.001) | 14.894 (<0.001) | AD<DS+; AD<DS-; DS HC<DS- |

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| normalised by TCV (% TCV) ** | | | | | | | | |
| Central corpus collosum | 0.35±0.1 | 0.38±0.1 | 0.5±0.13 | 0.28±0.07 | 0.33±0.08 | 6.962 (<0.001) | 4.510 (0.035) | AD<DS HC; AD HC<DS HC; DS+<DS HC; DS-<DS HC |
| Central corpus callosum normalised by TCV (% TCV) ** | 0.026±0.009 | 0.027±0.008 | 0.03±0.009 | 0.017±0.005 | 0.02±0.006 | 3.585 (0.008) | 19.361 (<0.001) | AD<DS-; AD<DS HC |
| Posterior corpus callosum** | 0.96±0.22 | 0.93±0.26 | 0.9±0.16 | 0.76±0.18 | 0.88±0.14 | 4.707 (0.001) | NS | AD<DS+; AD<DS-; AD<DS HC |
| Posterior corpus callosum normalised by TCV (% TCV) * | 0.071±0.02 | 0.066±0.02 | 0.051±0.009 | 0.047±0.01 | 0.057±0.01 | 14.852 (<0.001) | 14.454 (<0.001) | AD<DS+; AD<DS HC; AD HC<DS+; AD HC <DS-; DS HC<DS+; DS HC<DS- |
| Mid-posterior corpus callosum** | 0.381±0.11 | 0.382±0.09 | 0.44±0.1 | 0.27±0.06 | 0.32±0.07 | 4.049 (0.004) | NS | AD<DS HC |
| Mid-posterior corpus callosum normalised by TCV (% TCV) ** | 0.028±0.01 | 0.027±0.007 | 0.026±0.006 | 0.017±0.004 | 0.02±0.006 | 6.215 (<0.001) | 18.887 (<0.001) | AD<DS+; AD HC<DS+; AD<DS-; AD<DS HC |
| CSF* | 1.71±0.51 | 1.73±0.43 | 1.7±0.4 | 2.12±0.5 | 1.84±0.31 | 2.954 (0.022) | 23.313 (<0.001) | NS |
| CSF normalised by TCV (% TCV) ** | 0.125±0.03 | 0.119±0.02 | 0.1±0.02 | 0.131±0.02 | 0.119±0.002 | 4.507 (0.002) | 4.586 (0.034) | DS HC<DS+; DS HC<DS- |
| 3rd ventricle* | 1.3±0.49 | 1.09±0.38 | 0.95±0.32 | 2.15±0.7 | 1.48±0.54 | 7.302 (<0.001) | 35.186 (<0.001) | AD HC<AD; DS+<AD; DS-<AD; DS HC<AD |
| 3rd ventricle normalised by TCV (% TCV) * | 0.09±0.03 | 0.08±0.02 | 0.06±0.02 | 0.13±0.04 | 0.1±0.03 | 7.802 (<0.001) | 19.253 (<0.001) | AD HC<AD; DS-<AD; DS HC<AD; DS HC<DS+ |
| 4th ventricle** | 1.63±0.43 | 1.88±0.54 | 1.91±0.48 | 2.23±0.55 | 1.98±0.54 | 3.301 (0.013) | NS | DS+<AD; DS+<AD HC |
| 4th ventricle normalised by TCV (% TCV) ** | 0.12±0.04 | 0.13±0.04 | 0.11±0.03 | 0.14±0.04 | 0.13±0.03 | 4.151 (0.003) | NS | DS HC<DS- |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 5th ventricle* | 0.003±0.005 | 0.002±0.005 | 0.002±0.004 | 0.006±0.009 | 0.004±0.006 | NS | NS | NS |
| 5th ventricle normalised by TCV (% TCV) * | 0.0002±0.0003 | 0.0001±0.0003 | 0.0001±0.0002 | 0.0004±0.0005 | 0.0003±0.0004 | NS | NS | NS |
| Left inferior lateral ventricle* | 1.14±0.77 | 0.52±0.39 | 0.18±0.14 | 1.51±0.1 | 0.44±0.36 | 17.922 (<0.001) | NS | AD HC<AD; AD HC<DS+; DS-<AD; DS-<DS+; DS HC<AD; DS HC<DS+ |
| Left inferior lateral ventricle normalised by TCV (% TCV) * | 0.08±0.05 | 0.04±0.03 | 0.01±0.01 | 0.09±0.05 | 0.03±0.02 | 20.710 (<0.001) | NS | AD HC<AD; AD HC<DS+; DS HC<AD; DS HC<DS+; DS-<DS+ |
| Right inferior lateral ventricle* | 0.95±0.91 | 0.43±0.48 | 0.2±0.16 | 1.33±1.05 | 0.39±0.31 | 10.295 (<0.001) | NS | AD HC<AD; AD HC<DS |
| Right inferior lateral ventricle normalised by TCV (% TCV) ** | 0.07±0.06 | 0.03±0.03 | 0.01±0.01 | 0.08±0.06 | 0.03±0.02 | 11.510 (<0.001) | NS | AD HC<AD; AD HC<DS+; DS HC<DS+ |
| Left lateral ventricle* | 16.79±11.59 | 12.16±8.23 | 7.45±4.85 | 26.46±12.28 | 14.86±6.16 | 8.105 (<0.001) | 10.791 (0.001) | AD HC<AD; DS HC<AD |
| Left lateral ventricle normalised by TCV (% TCV) ** | 1.21±0.76 | 0.83±0.49 | 0.43±0.27 | 1.6±0.64 | 0.95±0.35 | 10.402 (<0.001) | 5.315 (0.023) | AD HC<AD; DS HC<AD; DS HC<DS+ |
| Right lateral ventricle** | 15.51±14.42 | 10.55±6.69 | 6.76±4.43 | 23.34±10.52 | 14.14±5.21 | 6.362 (<0.001) | 9.162 (0.003) | AD HC<AD; DS HC<AD |
| Right lateral ventricle normalised by TCV (% TCV) ** | 1.1±0.92 | 0.72±0.4 | 0.39±0.26 | 1.42±0.57 | 0.91±0.31 | 7.987 (<0.001) | 4.487 (0.036) | AD HC<AD; DS HC<AD; DS HC<DS+ |
| Left vessel ** | 0.04±0.05 | 0.03±0.03 | 0.06±0.03 | 0.06±0.04 | 0.05±0.03 | 3.778 (0.006) | NS | DS-<DS HC |
| Left vessel normalised by TCV (% TCV) * | 0.003±0.004 | 0.002±0.002 | 0.003±0.001 | 0.004±0.002 | 0.003±0.002 | 2.457 (0.048) | NS | NS |
| Right vessel** | 0.04±0.03 | 0.02±0.02 | 0.05±0.02 | 0.06±0.04 | 0.05±0.03 | 3.933 | NS | DS-<AD; DS-<DS HC |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | (0.005) | | |
| Right vessel normalised by TCV (% TCV) * | 0.003±0.003 | 0.001±0.001 | 0.003±0.001 | 0.004±0.002 | 0.003±0.002 | 2.791 (0.029) | NS | NS |
| Non-white matter hyperdensities* | 0.06±0.06 | 0.04±0.05 | 0.02±0.02 | 0.06±0.04 | 0.06±0.09 | NS | NS | NS |
| Non-white matter hyperdensities normalised by TCV (% TCV) * | 0.004±0.001 | 0.003±0.003 | 0.001±0.001 | 0.004±0.003 | 0.004±0.006 | NS | NS | NS |
| White matter hyperdensities** | 3.31±1.41 | 2.98±1.19 | 2.46±0.59 | 10.99±8.78 | 5.72±6.28 | 5.573 (<0.001) | NS | AD HC<AD; DS HC<AD; DS+<AD; DS-<AD |
| White matter hyperdensities normalised by TCV (% TCV) ** | 0.24±0.09 | 0.21±0.07 | 0.14±0.03 | 0.67±0.53 | 0.37±0.41 | 5.005 (0.001) | NS | AD HC<AD; DS HC<AD; DS+<AD |

* $p<0.001$; **$p<0.05$

***Table 3.2: Automated cortical volume study analysis***

### 3.2.3 Thickness measures (Table 3.3)

There was a significant main effect of gender for the caudal anterior cingulate cortex. Follow-up comparisons did not produce any significant results.

There was a significant main effect of group for the caudal middle frontal gyrus. Follow-up comparisons revealed a significant reduction in the caudal middle frontal gyrus thickness for AD compared to its non-demented control group. Within DS individuals, the reduction in thickness between DS+ and DS- (both -6%) was similar to that within AD cases and controls from the general population (respectively -7%).

There was a significant effect of gender for the corpus callosum. Follow-up comparisons did not reveal any significant results.

There was a significant main effect of group for the cuneus cortex. Follow-up comparisons revealed that AD had a significant reduction in cuneus cortex thickness compared to its non-demented control group. Within DS individuals, the reduction in thickness between DS+ and DS- (both -7%) was greater to that within AD cases and controls from the general population (respectively -9%).

There was a significant main effect of group for the entorhinal cortex. Follow-up comparisons revealed that AD had a significant reduction in entorhinal cortex thickness compared to its non-demented control group. The reduction in thickness between AD and its non-demented control group (-15%) was twice that between DS+ and DS- (-7%).

There was a significant main effect of group for the frontal operculum. Follow-up comparisons revealed that AD had a significant reduction in frontal operculum thickness compared to its non-demented control group. The reduction in thickness between AD and its non-demented control group (-8%) was greater than that between DS+ and DS- (-5%).

There was no significant main effect of either group or gender for the frontal pole. Follow-up comparisons did not produce any significant results.

There was a significant main effect of group for the fusiform gyrus. Follow-up comparisons revealed that AD had a significant reduction in fusiform gyrus thickness compared to its non-demented control group. The reduction in thickness between AD and its non-demented control group (-10%) was greater than that between DS+ and DS- (-6%).

There was a significant main effect of group for the inferior parietal cortex. Follow-up comparisons revealed that AD had a significant reduction in inferior parental cortex thickness compared to its non-demented control group. The reduction in thickness between AD and its non-demented control group (-10%) was greater than that between DS+ and DS- (-7%).

There was a significant main effect of group for the inferior temporal gyrus. Follow-up comparisons revealed that AD had a significant reduction in inferior temporal gyrus thickness compared to its non-demented control group. The reduction in

thickness between AD and its non-demented control group (-6%) was greater than that between DS+ and DS- (-4%).

There was a significant main effect of group for the isthmus of the cingulate cortex. Follow-up comparisons revealed that AD had a significant reduction in thickness of the isthmus of the cingulate cortex compared to its non-demented control group. The reduction in thickness between AD and its non-demented control group (-14%) was twice that between DS+ and DS- (-7%).

There was a significant main effect of group for the lateral occipital cortex. Follow-up comparisons revealed that AD had a significant reduction in lateral occipital cortex thickness compared to its non-demented control group. The reduction in thickness between AD and its non-demented control group (-7%) was greater than that between DS+ and DS- (-5%).

There was a significant main effect of group for the lateral occipital frontal cortex. Follow-up comparisons revealed that AD had a significant reduction in lateral occipital frontal cortex thickness compared to its non-demented control group. The reduction in thickness between AD and its non-demented control group (-8%) was greater than that between DS+ and DS- (-5%).

There was a significant main effect of group for the lingual gyrus. Follow-up comparisons revealed that AD had a significant reduction and DS+ had a significant increase in lateral occipital cortex thickness when compared to their respective non-

demented control groups. The reduction in thickness between AD and its non-demented control group (-7%) was more than twice that between DS+ and DS- (-3%).

There was a significant main effect of group for the middle orbital frontal gyrus. Follow-up comparisons revealed that AD had a significant reduction, and DS+ had a significant increase in middle orbital frontal thickness when compared to their respective non-demented control groups. The reduction in thickness between AD and its non-demented control group (-11%) was more than three times that between DS+ and DS- (-3%).

There was a significant main effect of group for the middle temporal gyrus. Follow-up comparisons revealed that AD had a significant reduction in middle temporal gyrus thickness when compared to its respective non-demented control group. The reduction in thickness between AD and its non-demented control group (-8%) was twice than that between DS+ and DS- (-4%).

There was a significant main effect of group and gender for the orbital operculum. Follow-up comparisons revealed that AD had a significant reduction in orbital operculum thickness when compared to its non-demented control group. The reduction in thickness between AD and its non-demented control group (-11%) was almost four times that between DS+ and DS- (-3%).

There was a significant main effect of group and gender for the paracentral sulcus. Follow-up comparisons revealed that AD had a significant reduction in paracentral sulcus thickness when compared to its non-demented control group. The reduction in

thickness between AD and its non-demented control group (-14%) was more than twice that between DS+ and DS- (-6%).

There was a significant main effect of group for the parahippocampal gyrus. Follow-up comparisons revealed that AD had a significant reduction in parahippocampal gyrus thickness when compared to its non-demented control group. The reduction in thickness between AD and its non-demented control group (-15%) was more than twice that between DS+ and DS- (-6%).

There was a significant main effect of group for the pericalcarine cortex. Follow-up comparisons revealed that AD had a significant reduction in pericalcarine cortical thickness when compared to its non-demented control group. The reduction in thickness between AD and its non-demented control group (-8%) was greater than that between DS+ and DS- (-5%).

There was a significant main effect of group and gender for the postcentral gyrus. Follow-up comparisons revealed that AD had a significant reduction in postcentral gyrus thickness when compared to its non-demented control group. The reduction in thickness between AD and its non-demented control group (-8%) was similar to that between DS+ and DS- (-7%).

There was a significant main effect of group for the posterior cingulate cortex. Follow-up comparisons revealed that AD had a significant reduction in posterior cingulate cortical thickness when compared to its non-demented control group. The

reduction in thickness between AD and its non-demented control group (-10%) was greater than that between DS+ and DS- (-7%).

There was a significant main effect of group and gender for the precentral gyrus. Follow-up comparisons revealed that AD had a significant reduction in precentral gyrus thickness when compared to its non-demented control group. The reduction in thickness between AD and its non-demented control group (-12%) was six times greater than that between DS+ and DS- (-2%).

There was a significant main effect of group for the precuneus gyrus. Follow-up comparisons revealed that AD had a significant reduction in precuneus gyrus thickness when compared to its non-demented control group. The reduction in thickness between AD and its non-demented control group (-10%) was greater than that between DS+ and DS- (-7%).

There was a significant main effect of group for the rostral anterior cingulate cortex. Follow-up comparisons did not reveal any significant findings.

There was a significant main effect of group for the rostral middle frontal gyrus. Follow-up comparisons revealed that AD had a significant reduction in rostral middle frontal gyrus thickness when compared to its non-demented control group. The reduction in thickness between AD and its non-demented control group (-11%) was almost four times greater than that between DS+ and DS- (-3%).

There was a significant main effect of group and gender for the superior frontal gyrus. Follow-up comparisons revealed that AD had a significant reduction in superior frontal gyrus thickness when compared to its non-demented control group. The reduction in thickness between AD and its non-demented control group (-9%) was more than twice that between DS+ and DS- (-4%).

There was a significant main effect of group and gender for the superior parietal cortex. Follow-up comparisons revealed that AD had a significant reduction in superior parietal cortical thickness when compared to its non-demented control group. The reduction in thickness between AD and its non-demented control group (-9%) was almost twice that between DS+ and DS- (-5%).

There was a significant main effect of group for the superior temporal gyrus. Follow-up comparisons revealed that AD had a significant reduction in superior temporal gyrus thickness when compared to its non-demented control group. The reduction in thickness between AD and its non-demented control group (-8%) was greater than that between DS+ and DS- (-5%).

There was a significant main effect of group for the supramarginal gyrus. Follow-up comparisons revealed that AD had a significant reduction in supramarginal gyrus thickness compared to its non-demented control group. The reduction in thickness between AD and its non-demented control group (-10%) was similar to that between DS+ and DS- (-9%).

There was no significant main effect of group or gender for the temporal pole. Follow-up comparisons did not reveal any significant results.

There was a significant main effect of group and gender for the transverse temporal cortex. Follow-up comparisons revealed that AD had a significant reduction in transverse temporal cortical thickness when compared to its non-demented control group. The reduction in thickness between AD and its non-demented control group (-11%) was almost three times that between DS+ and DS- (-4%).

There was a significant main effect of group for the triangular part of the inferior frontal gyrus. Follow-up comparisons revealed that AD had a significant reduction in thickness of the triangular part of the inferior frontal gyrus when compared to its non-demented control group. The reduction in thickness between AD and its non-demented control group (-8%) was twice that between DS+ and DS- (-4%).

| | DS+ (N=14) Mean ± SD | DS- (N=30) Mean ± SD | DS HC (N=40) Mean ± SD | AD (N=35) Mean ± SD | AD HC (N=37) Mean ± SD | F effect of group (p value) | F effect of gender (p value) | Significant pairwise comparisons |
|---|---|---|---|---|---|---|---|---|
| Caudal anterior cingulate cortex | 2.83±0.24 | 2.92±0.3 | 2.87±0.23 | 2.59±0.38 | 2.82±0.31 | NS | 4.937 (0.028) | NS |
| Caudal middle frontal gyrus** | 2.61±0.26 | 2.77±0.22 | 2.64±0.13 | 2.31±0.21 | 2.49±0.16 | 10.081 (<0.001) | NS | AD<DS+; AD<DS-; AD<AD HC; AD<DS HC; AD HC<DS-; DS HC<DS- |
| Corpus callosum* | 0.51±0.0 | 0.53±0.09 | 0.56±0.06 | 0.5±0.09 | 0.55±0.08 | NS | 4.905 (0.028) | NS |
| Cuneus cortex* | 1.97±0.2 | 2.04±0.23 | 1.92±0.15 | 1.56±0.19 | 1.72±0.19 | 8.109 (<0.001) | NS | AD<AD HC; AD<DS+; AD<DS- |
| Entorhinal cortex* | 2.96±0.2 | 3.18±0.4 | 3.05±0.31 | 2.63±0.37 | 3.1±0.34 | 8.227 (<0.001) | NS | AD<AD HC; AD<DS+; AD<DS-; AD<DS HC |
| Frontal operculum* | 2.64±0.27 | 2.78±0.19 | 2.7±0.14 | 2.32±0.19 | 2.51±0.2 | 9.047 (<0.001) | NS | AD<AD HC; AD<DS+; AD<DS-; AD<DS HC |
| Frontal pole* | 3.29±0.38 | 3.38±0.3 | 3.39±0.36 | 2.98±0.46 | 3.22±0.41 | NS | NS | NS |
| Fusiform gyrus* | 2.61±0.23 | 2.77±0.14 | 2.74±0.15 | 2.36±0.19 | 2.63±0.19 | 12.298 (<0.001) | NS | AD<AD HC; AD<DS+; AD<DS-; AD<DS HC |
| Inferior parietal cortex* | 2.43±0.27 | 2.62±0.18 | 2.54±0.12 | 2.15±0.2 | 2.39±0.16 | 12.911 (<0.001) | NS | AD<DS+; AD<DS-; AD<AD HC; AD<DS HC; DS+<DS- |
| Inferior temporal gyrus* | 2.85±0.23 | 2.96±0.19 | 2.89±0.15 | 2.74±0.21 | 2.93±0.15 | 6.455 (<0.001) | NS | AD<AD HC; AD<DS- |
| Isthmus of cingulate cortex* | 2.6±0.23 | 2.8±0.2 | 2.79±0.2 | 2.24±0.25 | 2.61±0.2 | 14.116 (<0.001) | NS | AD<AD HC; AD<DS+; AD<DS-; AD<DS HC |
| Lateral occipital cortex* | 2.35±0.12 | 2.48±0.18 | 2.27±0.13 | 2.02±0.15 | 2.18±0.17 | 16.860 (<0.001) | NS | AD<AD HC; AD<DS+; AD<DS-; AD HC<DS-; DS HC<DS- |
| Lateral occipital frontal cortex* | 2.9±0.23 | 3.04±0.18 | 2.88±0.14 | 2.51±0.2 | 2.74±0.21 | 12.881 (<0.001) | NS | AD<AD HC; AD<DS+; AD<DS-; DS HC<DS- |
| Lingual gyrus** | 2.17±0.17 | 2.23±0.14 | 2.07±0.13 | 1.74±0.15 | 1.87±0.13 | 17.972 (<0.001) | NS | AD<AD HC; AD<DS+; AD<DS-; AD HC<DS+; AD HC<DS-; DS HC<DS+; DS HC<DS- |
| Medial orbital | 3.18±0.33 | 3.28±0.31 | 2.87±0.26 | 2.52±0.28 | 2.84±0.26 | 18.880 | NS | AD<AD HC; AD<DS+; |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| frontal gyrus* | | | | | | (<0.001) | | AD<DS-; DS HC<DS+; DS HC<DS- |
| Middle temporal gyrus* | 2.9±0.27 | 3.02±0.17 | 2.98±0.13 | 2.64±0.24 | 2.88±0.2 | 5.751 (<0.001) | NS | AD<AD HC |
| Orbital operculum* | 3.02±0.43 | 3.1±0.32 | 2.91±0.2 | 2.45±0.23 | 2.74±0.27 | 9.870 (<0.001) | 6.076 (0.015) | AD<AD HC; AD<DS+; AD<DS- |
| Paracentral sulcus* | 2.34±0.35 | 2.5±0.24 | 2.5±0.12 | 1.98±0.3 | 2.31±0.21 | 9.324 (<0.001) | 5.511 (0.020) | AD<AD HC; AD<DS-; AD<DS HC |
| Parahippocampal gyrus* | 2.67±0.29 | 2.85±0.22 | 2.59±0.3 | 2.06±0.32 | 2.43±0.22 | 14.035 (<0.001) | NS | AD<AD HC; AD<DS+; AD<DS-; AD<DS HC; DS HC<DS- |
| Pericalcarine cortex** | 1.59±0.14 | 1.67±0.17 | 1.64±0.11 | 1.35±0.12 | 1.46±0.12 | 5.443 (<0.001) | NS | AD<AD HC; AD<DS+; AD<DS-; AD<DS HC |
| Postcentral gyrus* | 2.12±0.2 | 2.29±0.2 | 2.15±0.12 | 1.88±0.18 | 2.05±0.16 | 9.805 (<0.001) | 7.275 (0.008) | AD<AD HC; AD<DS-; DS HC<DS- |
| Posterior cingulate cortex* | 2.5±0.25 | 2.68±0.18 | 2.61±0.18 | 2.17±0.2 | 2.4±0.22 | 7.363 (<0.001) | NS | AD<AD HC; AD<DS- |
| Precentral gyrus* | 2.36±0.27 | 2.4±0.26 | 2.58±0.11 | 2.12±0.21 | 2.42±0.15 | 11.376 (<0.001) | 6.241 (0.014) | AD<AD HC; AD<DS HC |
| Precuneus cortex | 2.32±0.32 | 2.49±0.17 | 2.4±0.13 | 1.99±0.23 | 2.22±0.18 | 9.095 (<0.001) | NS | AD<AD HC; AD<DS+; AD<DS- |
| Rostral anterior cingulate cortex* | 3.03±0.32 | 3.21±0.31 | 3.08±0.23 | 2.82±0.34 | 3.04±0.28 | 2.850 (0.026) | NS | NS |
| Rostral middle frontal gyrus* | 2.76±0.23 | 2.83±0.18 | 2.73±0.12 | 2.28±0.19 | 2.56±0.18 | 19.167 (<0.001) | NS | AD<AD HC; AD<DS+; AD<DS-; AD HC<DS-; AD<DS HC |
| Superior frontal gyrus* | 3.03±0.35 | 3.16±0.23 | 2.95±0.13 | 2.48±0.21 | 2.71±0.18 | 19.046 (<0.001) | 6.474 (0.012) | AD<AD HC; AD<DS+; AD<DS-; AD<DS HC; AD HC<DS-; DS HC<DS- |
| Superior parietal cortex** | 2.18±0.23 | 2.3±0.18 | 2.19±0.97 | 1.93±0.21 | 2.11±0.15 | 8.097 (<0.001) | 5.004 (0.027) | AD<AD HC; AD<DS-; DS HC<DS- |
| Superior temporal gyrus* | 2.57±0.23 | 2.7±0.15 | 2.77±0.15 | 2.32±0.21 | 2.52±0.18 | 5.070 (0.001) | NS | AD<AD HC |
| Supramarginal gyrus** | 2.47±0.29 | 2.71±0.15 | 2.59±0.13 | 2.2±0.18 | 2.43±0.16 | 14.092 (<0.001) | NS | AD<AD HC; AD<DS+; AD<DS-; AD<DS HC; |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | DS+<DS-; DS HC<DS- |
| Temporal pole* | 3.5±0.38 | 3.46±0.47 | 3.62±0.36 | 3.29±0.41 | 3.55±0.28 | NS | NS | NS |
| Transverse temporal cortex** | 2.14±0.21 | 2.23±0.28 | 2.41±0.22 | 1.91±0.25 | 2.14±0.24 | 4.801 (0.001) | 5.366 (0.022) | AD<AD HC |
| Triangular part of inferior frontal gyrus* | 2.71±0.22 | 2.81±0.22 | 2.75±0.17 | 2.3±0.18 | 2.49±0.19 | 9.410 (<0.001) | NS | AD<AD HC; AD<DS+; AD<DS-; AD<DS HC; AD HC<DS- |

* $p<0.001$; ** $p<0.05$

***Table 3.3: Automated thickness study analysis***

### 3.2.4 Relationship of cognitive ability to brain anatomy

As expected, DS+ had the lowest scores on both the MMSE and CAMCOG compared to the non-demented populations ($p \leq 0.001$). The DS+ group also showed significantly lower MMSE scores than the AD group ($p < 0.001$).

In the Alzheimer's disease population there was a positive correlation between MMSE and the following regions corrected for TCV: left and right hippocampus ($r$ 0.397, p 0.001 and $r$ 0.453, $p < 0.001$ respectively), left and right amygdala ($r$ 0.476, $p < 0.001$ and $r$ 0.524, $p < 0.001$ respectively), left and right thalamus ($r$ 0.309, p 0.009 and $r$ 0.260, p 0.03 respectively), left and right putamen ($r$ 0.307, p 0.01 and $r$ 0.298, p 0.012 respectively), left and right cerebellar cortex ($r$ 0.311, p 0.009 and $r$ 0.322 and p 0.007 respectively), left and right cerebral cortex ($r$ 0.371, p 0.02 and $r$ 0.387, p 0.001 respectively), anterior corpus callosum ($r$ 0.266, p 0.026), mid-anterior corpus callosum ($r$ 0.304, p 0.01), central corpus callosum ($r$ 0.303, p 0.011), posterior corpus callosum ($r$ 0.369, p 0.002) and mid-posterior corpus callosum ($r$ 0.408, $p < 0.001$).

There was a negative correlation for the Alzheimer's disease population between MMSE and the following regions corrected for TCV: optic chiasm ($r$ -0.299, p 0.012), CSF ($r$ -0.262, p 0.029), third ventricle ($r$ -0.265, p 0.027), left and right lateral ventricles ($r$ -0.317, p 0.08 and $r$ -0.0267, p 0.025), and left and right inferior lateral ventricles ($r$ -0.0403, p 0.001 and $r$ -0.426, $p < 0.001$ respectively).

In the Down's syndrome population there was a positive correlation between CAMCOG and the following regions corrected for TCV: left and right hippocampus (*r* 0.328, p 0.007 and *r* 0.358, p 0.003 respectively), left and right thalamus (*r* 0.248, p 0.043 and *r* 0.272, p 0.026 respectively), brainstem (*r* 0.633, p <0.001), left and right cerebellar cortex (*r* 0.587, p <0.001 and *r* 0.549, p <0.001 respectively), left and right cerebellar white matter (*r* 0.63, p <0.001 and *r* 0.619, p <0.001 respectively), left and right cerebral white matter (*r* 0.291, p 0.017 and *r* 0.279, p 0.022 respectively), left accumbens (*r* 0.394, p 0.001) and central corpus callosum (*r* 0.293, p 0.016).

There was a negative correlation for the Down's syndrome population between CAMCOG and the following regions corrected for TCV: left caudate (r -0.253, p 0.039), third ventricle (*r* -0.548, p <0.001), post central corpus callosum (*r* -0.264, p 0.031), CSF (*r* -0.452, p <0.001), left and right inferior lateral ventricle (*r* -0.621, p <0.001 and *r* -0.49, p <0.001 respectively), left and right ventricle (*r* -0.0554, p <0.001 and *r* -0.0508, p <0.001 respectively) , white matter hyperdensities (*r* -0.602, p <0.001) and non-white matter hyperdensities (*r* -0.383, p 0.001).

## 3.3 Magnetic resonance imaging of subjects with Alzheimer's disease, mild cognitive impairment and Alzheimer's disease healthy controls, scanned at baseline and re-scanned at 12 months (Table 3.4)

### 3.3.1 Raw (uncorrected) volumes

There was a significant main effect of group at baseline ($T_1$) and follow-up ($T_2$) for the volume of the WBV, total hippocampus, left and right hippocampus, total temporal lobe, left temporal lobe, total lateral ventricle and the left and right lateral ventricle. There was a significant main effect of group at $T_1$ but not $T_2$ for the volume of the right temporal lobe. There was a significant main effect of gender at $T_1$ and $T_2$ for the volume of WBV, TCV, total temporal lobes and the left and right temporal lobe.

There was a significant reduction between $T_1$ and $T_2$ for subjects with Alzheimer's disease, in total hippocampal volume (t 2.821, p 0.011) and total temporal lobe volume (t 2.281, p 0.034), and a significant increase in total lateral ventricle (t 3.870, p 0.001).

Follow-up pairwise comparisons revealed that the volume of the total hippocampus in addition to the left and right hippocampus showed a significant reduction in the AD group compared to MCI and AD HC at both $T_1$ and $T_2$. Figure 3.9 shows the hippocampal volumes for the AD, MCI and AD HC at $T_1$ and $T_2$.

The volume of the total temporal lobes in addition to left and right temporal lobe showed a significant reduction in the AD group compared to AD HC at $T_1$. The volume of the total temporal lobe and the left temporal lobe but not right temporal lobe also showed a significant reduction in AD compared to AD HC at $T_2$. A significant reduction in the AD group compared to MCI was shown for the total temporal lobe at both $T_1$ and $T_2$ and for the right temporal lobe at $T_1$. Figure 3.10 shows the temporal lobe volumes for the AD, MCI and AD HC at $T_1$ and $T_2$.

The volume of the total lateral ventricles in addition to left and right lateral ventricle showed a significant increase in the AD group compared to AD HC at both $T_1$ and $T_2$. Figure 3.11 shows the lateral ventricle volumes for the AD, MCI and AD HC at $T_1$ and $T_2$.

The AD group had a significant reduction in WBV at $T_1$ and $T_2$ compared to MCI and AD HC.

Within AD individuals between $T_1$ and $T_2$, there was a 7% reduction in volume of the hippocampus, a 3% reduction in the volume of the temporal lobe and a 22% increase in the volume of the lateral ventricle.

Within MCI individuals between $T_1$ and $T_2$, there was a 1% reduction in the volume of the hippocampus, a 0.2% reduction in the volume of the temporal lobe and a 9% increase in the volume of the lateral ventricles.

Within AD HC individuals between $T_1$ and $T_2$, there was a 4% reduction in the volume of the hippocampus, a 5% reduction in the volume of the temporal lobe and a 0.4% increase in the volume of the lateral ventricles.

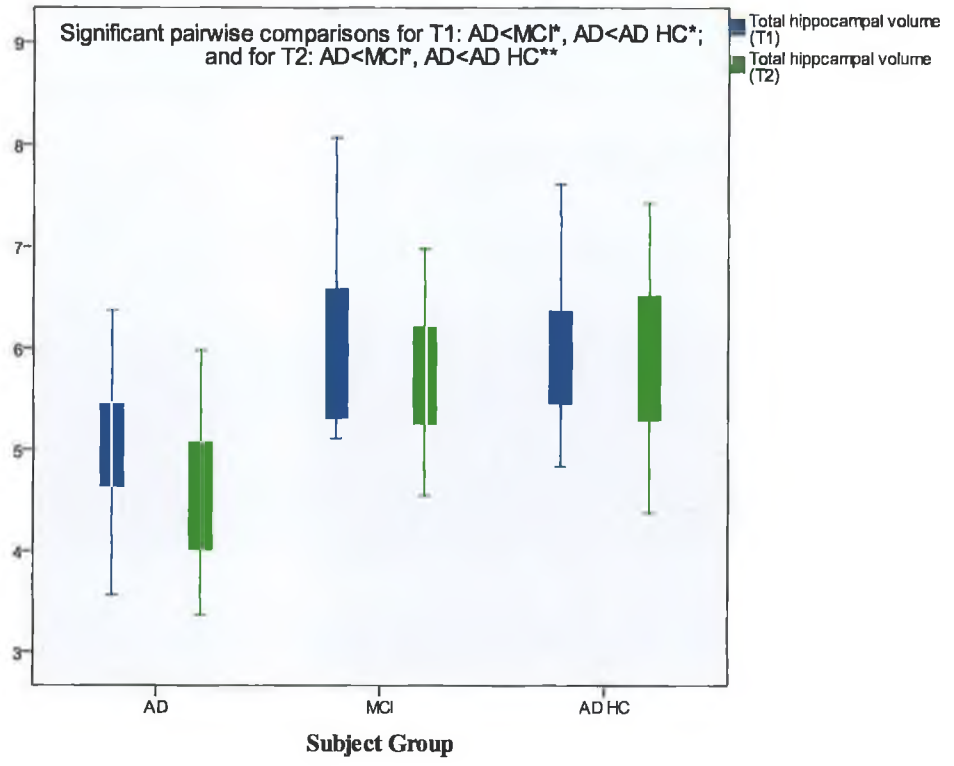


*Figure 3.9: Total hippocampal volume at $T_1$ and $T_2$*

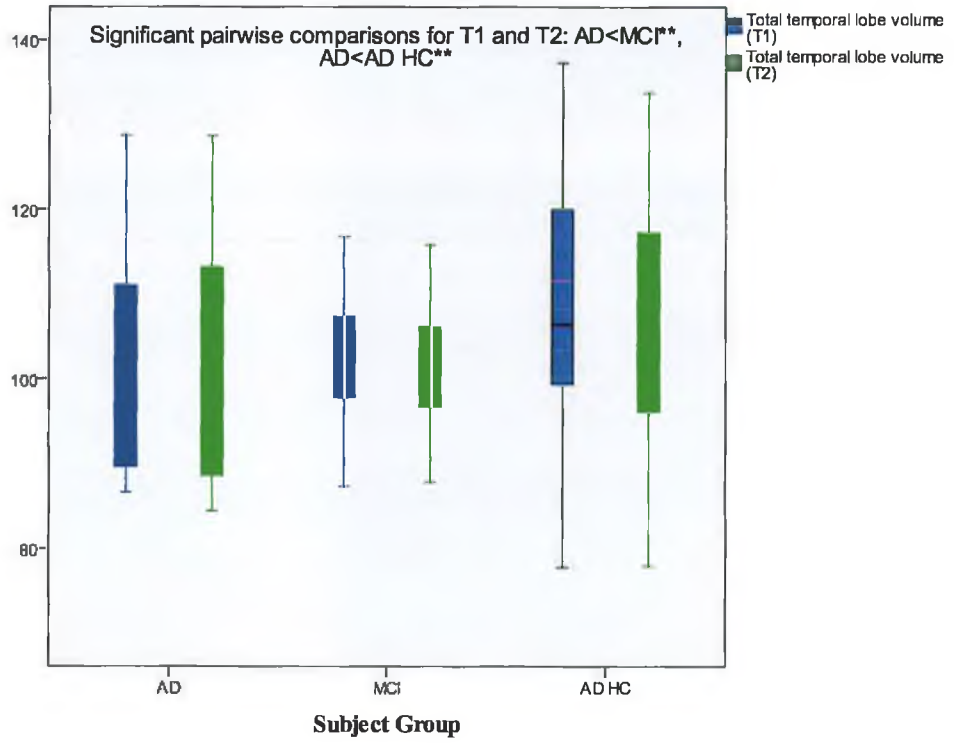


*Figure 3.10: Total temporal lobe volume at $T_1$ and $T_2$*

* p <0.001; Error bars represent SD

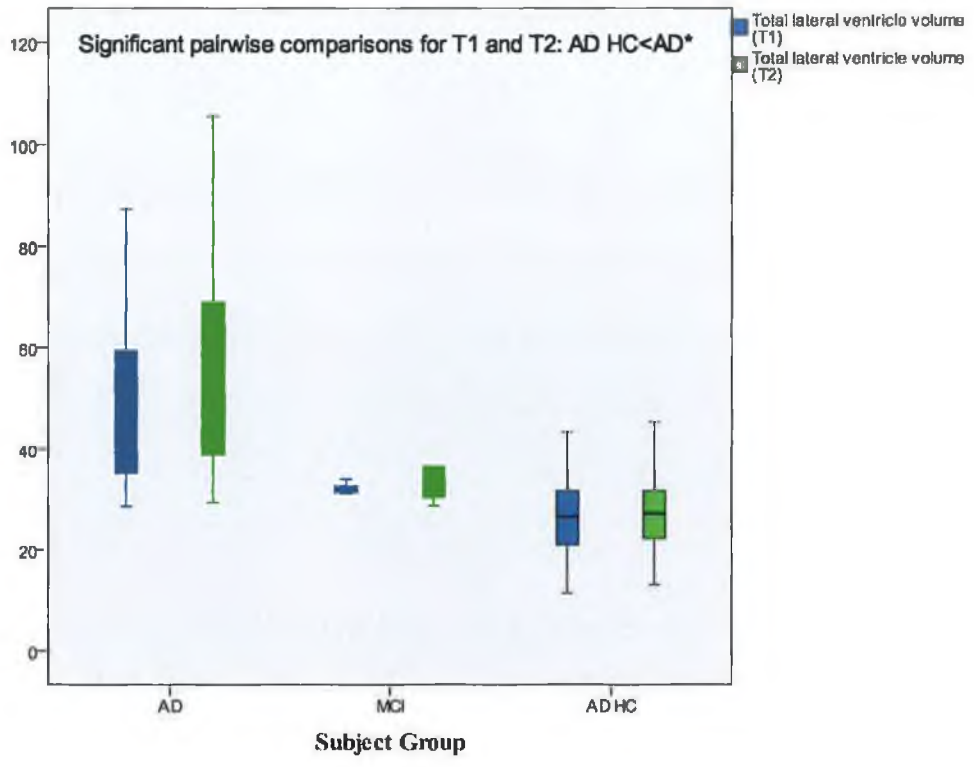


***Figure 3.11: Total lateral ventricle volume at $T_1$ and $T_2$***

* p <0.001; Error bars represent SD

### 3.3.2 Volumes corrected for total cranial volume

There was a significant main effect of group at $T_1$ and $T_2$ for the volume of the total hippocampus, left and right hippocampus, total temporal lobe, left temporal lobe, total lateral ventricles and the left and right lateral ventricles. There was a significant main effect of group at $T_1$ but not $T_2$ for the volume of the right temporal lobe. There was no significant main effect of gender.

Follow-up pairwise comparisons revealed that there was a significant reduction in the volume of the total hippocampus and the left and right hippocampus in the AD group compared to MCI and AD HC at both $T_1$ and $T_2$. Figure 3.12 shows the corrected hippocampal volumes for the AD, MCI and AD HC at $T_1$ and $T_2$.

There was a significant reduction in the volume of the total temporal lobe and the left temporal lobe in the AD group compared to AD HC at both $T_1$ and $T_2$. The total temporal lobe showed a significant reduction in the AD group compared to MCI at both $T_1$ and $T_2$. The right temporal lobe showed a significant reduction in the volume of AD group compared to AD HC at $T_1$ but not $T_2$. Figure 3.13 shows the corrected temporal lobe volumes for the AD, MCI and AD HC at $T_1$ and $T_2$.

There was a significant increase in the volume of the total lateral ventricles and the left and right lateral ventricles in the AD group compared to AD HC at both $T_1$ and $T_2$. There was also a significant increase in the total lateral ventricles in the AD group compared to MCI at $T_2$ and for the right lateral ventricles at both $T_1$ and $T_2$. Figure

3.14 shows the corrected lateral ventricle volumes for the AD, MCI and AD HC at $T_1$ and $T_2$.

Within AD individuals between $T_1$ and $T_2$, there was a 5% reduction in the volume of the hippocampus, a 1% reduction in the volume of the temporal lobe and a 23% increase in the volume of the lateral ventricles.

Within MCI individuals between $T_1$ and $T_2$, there was a 0.4% reduction in the volume of the hippocampus and a 10% increase in the volume of the lateral ventricles.

Within AD HC individuals between $T_1$ and $T_2$, there was a 2% reduction in the volume of the hippocampus, a 3% reduction in the volume of the temporal lobes and a 0.4% increase in the volume of the lateral ventricles.

### 3.3.3 Relationship of cognitive ability to brain anatomy

There was a positive correlation between MMSE and the corrected hippocampal volume at $T_1$ ($r$ 0.287, p 0.002) and $T_2$ (r 0.328, p 0.011) and between MMSE and the corrected temporal lobe volume at $T_1$ ($r$ 0.325, p <0.001) and $T_2$ (r 0.248, p 0.05). There was a negative correlation between MMSE and the corrected lateral ventricle volume at $T_1$ ($r$ - 0.417, p <0.001) and $T_2$ (r -0.532, p < 0.001).

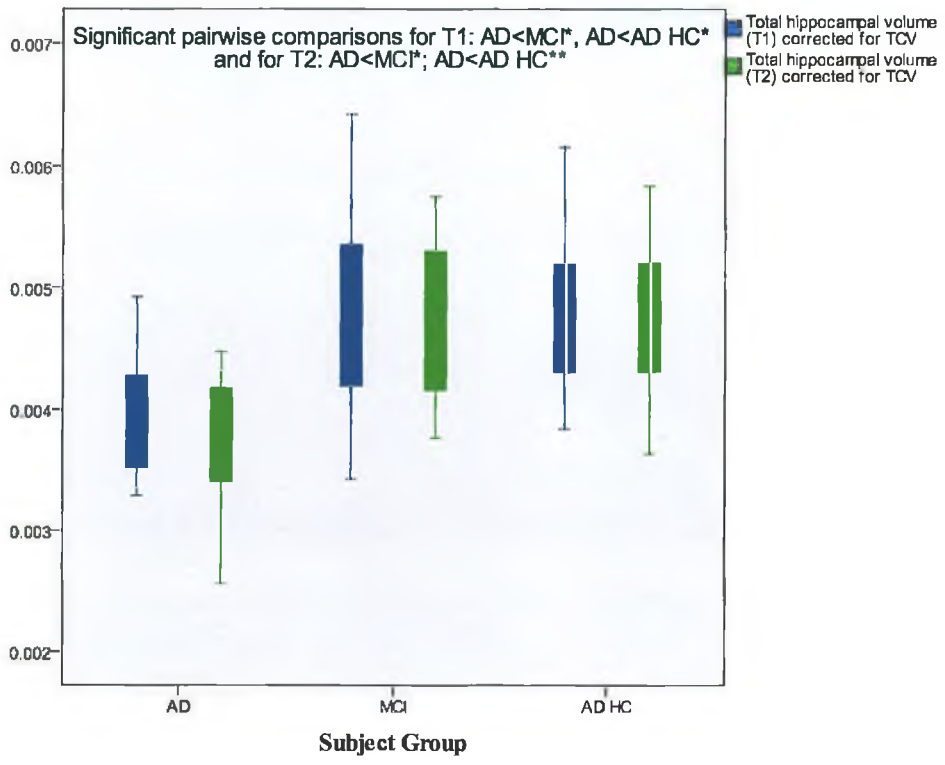


***Figure 3.12: Total hippocampal volume corrected for TCV at $T_1$ and $T_2$***

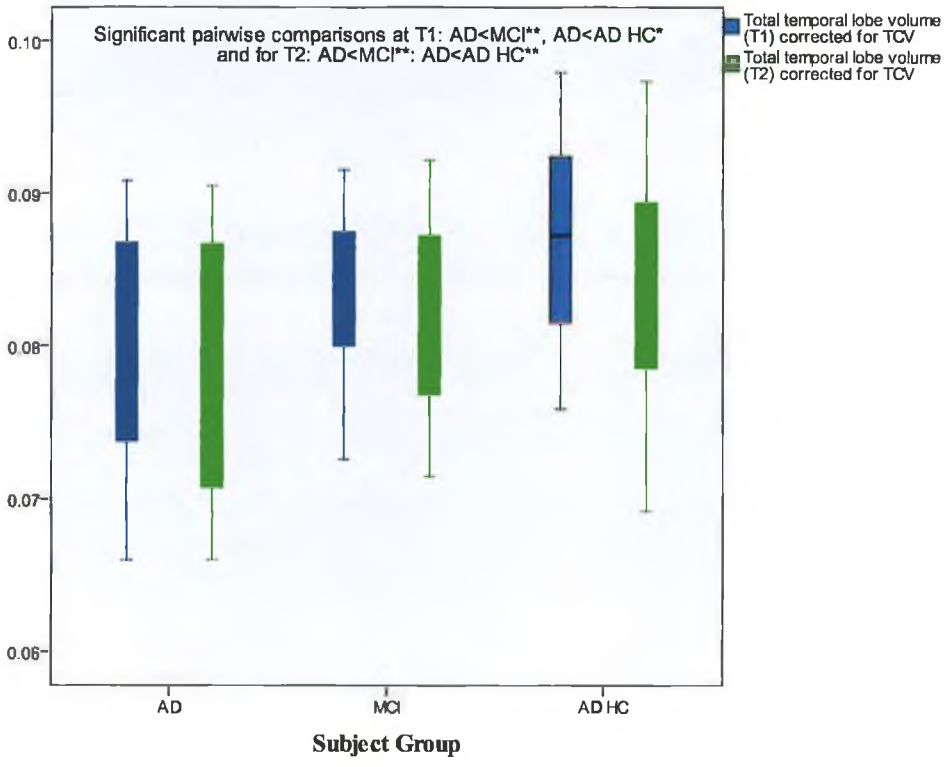


***Figure 3.13: Total temporal lobe volume corrected for TCV at $T_1$ and $T_2$***

* p <0.001; Error bars represent SD

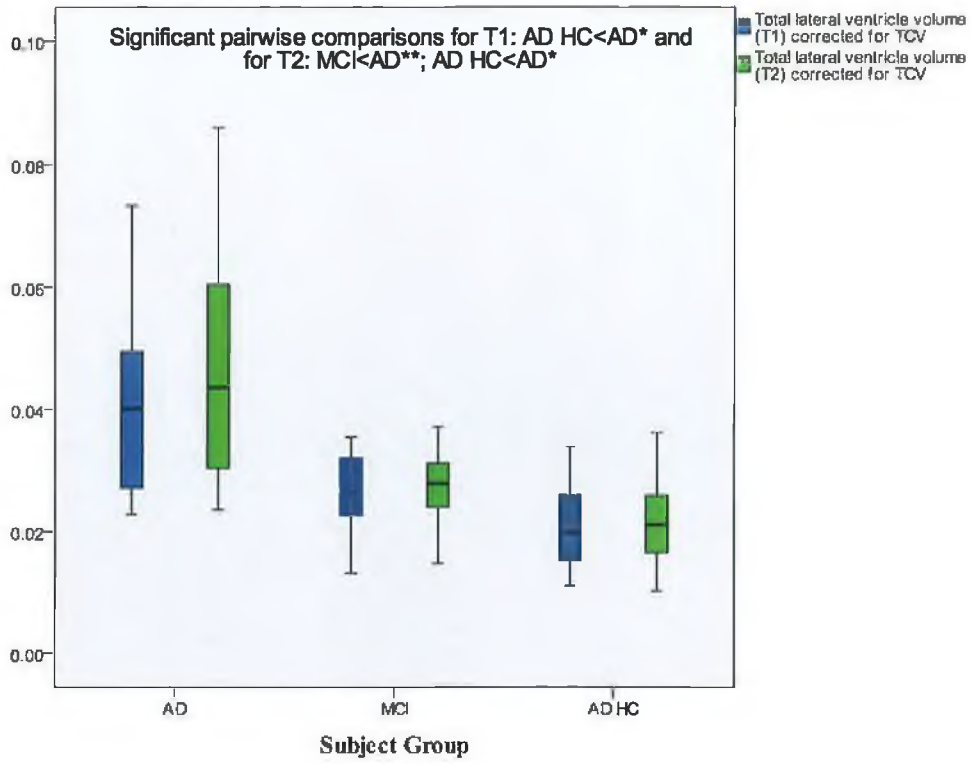


***Figure 3.14: Lateral ventricle volume corrected for TCV at $T_1$ and $T_2$***

* p <0.001; Error bars represent SD

| | | **AD (N for $T_1$=46) (N for $T_2$=20) Mean ± SD** | **MCI (N for $T_1$=28) (N for $T_2$=17) Mean ± SD** | **AD HC (N for $T_1$=39) (N for $T_2$=23) Mean ± SD** | **F effect of group (p value)** | **F effect of gender (p value)** | **Significant pairwise comparisons** |
|---|---|---|---|---|---|---|---|
| Age (years) | | 76.59±5.3 | 78.21±5.3 | 75.87±5.5 | NS | NS | NS |
| Education (years) | | 11.13±3.22 | 10.46±2.4 | 11.49±3 | NS | NS | NS |
| Sex (F:M) | | 24:22 | 17:11 | 28:11 | | | |
| MMSE | | 22.48±3.67 | 26.39±1.73 | 28.74±3.23 | 36.704 (<0.001) | NS | AD<MCI*; AD<AD HC* |
| WBV | $T_1$ | 904.32±83.304 | 929.098±85.777 | 930.767±77.411 | 3.745 (0.027) | 25.177 (<0.001) | AD<MCI**; AD<AD HC** |
| | $T_2$ | 859.099±74.529 | 913.211±93.899 | 915.484±87.078 | 6.876 (0.002) | 14.943 (<0.001) | AD<MCI**; AD<AD HC** |
| TCV | $T_1$ | 1.293±109.274 | 1.293±114.206 | 1.277±97.947 | NS | 44.716 (<0.001) | NS |
| | $T_2$ | 1.27±106.358 | 1.281±125.738 | 1.259±101.334 | NS | 15.155 (<0.001) | NS |
| Hippocampus | $T_1$ | 5.116±1.039 | 5.947±1.062 | 6.192±0.854 | 15.922 (<0.001) | NS | AD<MCI*; AD<AD HC* |
| | $T_2$ | 4.756±0.842 | 5.871±0.849 | 5.928±0.884 | 10.704 (<0.001) | NS | AD<MCI*; AD<AD HC** |
| Hippocampal volume normalised by TCV (%TCV) | $T_1$ | 0.396±0.07 | 0.461±0.078 | 0.486±0.063 | 16.195 (<0.001) | NS | AD<MCI*; AD<AD HC* |
| | $T_2$ | 0.374±0.056 | 0.459±0.06 | 0.472±0.066 | 10.660 (<0.001) | NS | AD<MCI*; AD<AD HC** |
| Left hippocampus (ml) | $T_1$ | 2.6246±0.515 | 2.9837±0.6171 | 3.171±0.4564 | 13.437 (<0.001) | NS | AD<MCI**; AD<AD HC* |
| | $T_2$ | 2.4545±0.4701 | 3.0411±0.3851 | 3.043±0.4966 | 10.579 (<0.001) | NS | AD<MCI*; AD<AD HC** |
| Left hippocampus normalised by TCV (%TCV) | $T_1$ | 0.203±0.0354 | 0.231±0.044 | 0.249±0.032 | 14.014 (<0.001) | NS | AD<MCI**; AD<AD HC* |
| | $T_2$ | 0.193±0.029 | 0.236±0.0239 | 0.242±0.036 | 11.458 (<0.001) | NS | AD<MCI*; AD<AD HC** |
| Right hippocampus (ml) | $T_1$ | 2.481±0.576 | 2.963±0.487 | 3.019±0.439 | 15.840 (<0.001) | NS | AD<MCI*; AD<AD HC* |
| | $T_2$ | 2.301±0.449 | 2.856±0.499 | 2.884±0.442 | 8.338 (0.001) | NS | AD<MCI**; AD<AD HC** |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Right hippocampus normalised by TCV (%TCV) | $T_1$ | 0.192±0.04 | 0.23±0.038 | 0.237±0.034 | 15.448 (<0.001) | NS | AD<MCI*; AD<AD HC* |
| | $T_2$ | 0.181±0.033 | 0.224±0.038 | 0.23±0.035 | 7.479 (0.001) | NS | AD<MCI**; AD<AD HC** |
| Temporal lobes (ml) | $T_1$ | 101.772±15 | 105.678±13.055 | 110.566±14.21 | 7.683 (0.001) | 23.314 (<0..001) | AD<MCI**; AD<AD HC** |
| | $T_2$ | 98.81±13.725 | 105.478±14.383 | 105.386±14.548 | 4.589 (0.015) | 11.904 (0.001) | AD<MCI**; AD<AD HC** |
| Temporal lobes normalised by TCV (%TCV) | $T_1$ | 7.861±0.813 | 8.168±0.653 | 8.65±0.8 | 10.321 (<0.001) | NS | AD<MCI**; AD<AD HC* |
| | $T_2$ | 7.78±0.834 | 8.224±0.664 | 8.356±0.798 | 3.999 (0.024) | NS | AD<MCI**; AD<AD HC** |
| Left temporal lobe (ml) | $T_1$ | 51.967±8.352 | 53.106±8.4 | 56.735±9.609 | 4.696 (0.011) | 10.627 (0.001) | AD<AD HC** |
| | $T_2$ | 50.049±8.815 | 52.869±7.936 | 54.387±8.873 | 4.572 (0.015) | 13.344 (0.001) | AD<AD HC** |
| Left temporal lobe normalised by TCV (%TCV) | $T_1$ | 4.015±0.5125 | 4.106±0.538 | 4.43±0.581 | 5.344 (0.006) | NS | AD<AD HC** |
| | $T_2$ | 3.939±0.584 | 4.122±0.42 | 4.31±0.499 | 3.873 (0.027) | NS | AD<AD HC** |
| Right temporal lobe (ml) | $T_1$ | 49.803±9.136 | 52.572±7.531 | 53.825±7.21 | 5.074 (0.008) | 19.04 (<0.001) | AD<MCI**; AD<AD HC** |
| | $T_2$ | 48.762±7.231 | 52.609±7.553 | 50.999±7.896 | NS | 4.778 (0.033) | NS |
| Right temporal lobe normalised by TCV (%TCV) | $T_1$ | 3.846±0.571 | 4.062±0.422 | 4.219±0.512 | 5.182 (0.007) | NS | AD<AD HC** |
| | $T_2$ | 3.843±0.475 | 4.101±0.381 | 4.048±0.527 | NS | NS | NS |
| Lateral ventricles (ml) | $T_1$ | 48.996±21.808 | 41.114±20.158 | 27.723±12.273 | 10.09 (<0.001) | NS | AD HC<AD* |
| | $T_2$ | 62.845±27.146 | 45.222±23.742 | 27.24±9.291 | 10.952 (<0.001) | NS | AD HC<AD* |
| Lateral ventricles normalised by TCV (%TCV) | $T_1$ | 3.8±1.65 | 3.17±1.498 | 2.162±0.891 | 11.334 (<0.001) | NS | AD HC<AD* |
| | $T_2$ | 4.946±2.072 | 3.511±1.771 | 2.171±0.752 | 12.445 (<0.001) | NS | MCI<AD**; AD HC<AD* |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Left lateral ventricle (ml) | $T_1$ | 22.684±10.748 | 20.268±9.799 | 13.6±6.0659 | 7.82 (0.001) | NS | AD HC<AD* |
| | $T_2$ | 29.315±12.388 | 24.354±20.128 | 14.219±7.195 | 5.026 (0.01) | NS | AD HC<AD** |
| Left lateral ventricle normalised by TCV (%TCV) | $T_1$ | 1.761±0.822 | 1.567±0.742 | 1.062±0.447 | 8.588 (<0.001) | NS | AD HC<AD* |
| | $T_2$ | 2.313±0.958 | 1.892±1.515 | 1.133±0.573 | 5.707 (0.006) | NS | AD HC<AD** |
| Right lateral ventricle (ml) | $T_1$ | 26.169±11.634 | 21.365±11.757 | 14.112±6.698 | 10.564 (<0.001) | NS | AD HC<AD* |
| | $T_2$ | 33.535±15.943 | 23.89±14.825 | 13.935±5.263 | 9.277 (<0.001) | NS | AD HC<AD* |
| Right lateral ventricle (ml) normalised by TVC (%TCV) | $T_1$ | 2.028±0.88 | 1.641±0.856 | 1.1±0.484 | 11.948 (<0.001) | NS | MCI<AD**; AD HC<AD* |
| | $T_2$ | 2.632±1.218 | 1.847±1.088 | 1.11±0.419 | 10.574 (<0.001) | NS | MCI<AD**; AD HC<AD* |

* $p < 0.001$; ** $p < 0.05$

***Table 3.4: Magnetic resonance imaging of subjects with Alzheimer's disease, mild cognitive impairment and Alzheimer's disease healthy controls, scanned at baseline ($T_1$) and re-scanned at 12 months ($T_2$)***

## 3.4 Magnetic resonance spectroscopy (Table 3.5)

### 3.4.1 N-acetyl aspartate [NAA]

There was a significant main effect of group and gender.

Follow-up comparisons revealed that the AD group had a significant reduction in [NAA] compared to the age appropriate AD HC group ($p<0.001$) but not when compared to DS+ or younger DS HC groups. No other follow-up comparisons were significant. Figure 3.15 shows the mean hippocampal [NAA] for AD, AD HC, DS+, DS- and DS HC.

Percentage reductions in adjusted [NAA] levels were at -12% for the AD group when compared to their age appropriate AD HC (adjusted for age and grey and white matter proportions of the MRS voxel). For comparison purposes, there was a -11% reduction in adjusted [NAA] levels for the DS+ group when compared to the age appropriate DS HC.

AD had a -16% reduction in adjusted [NAA] when compared to DS-, in comparison to a -8% reduction when DS+ was compared to DS-.

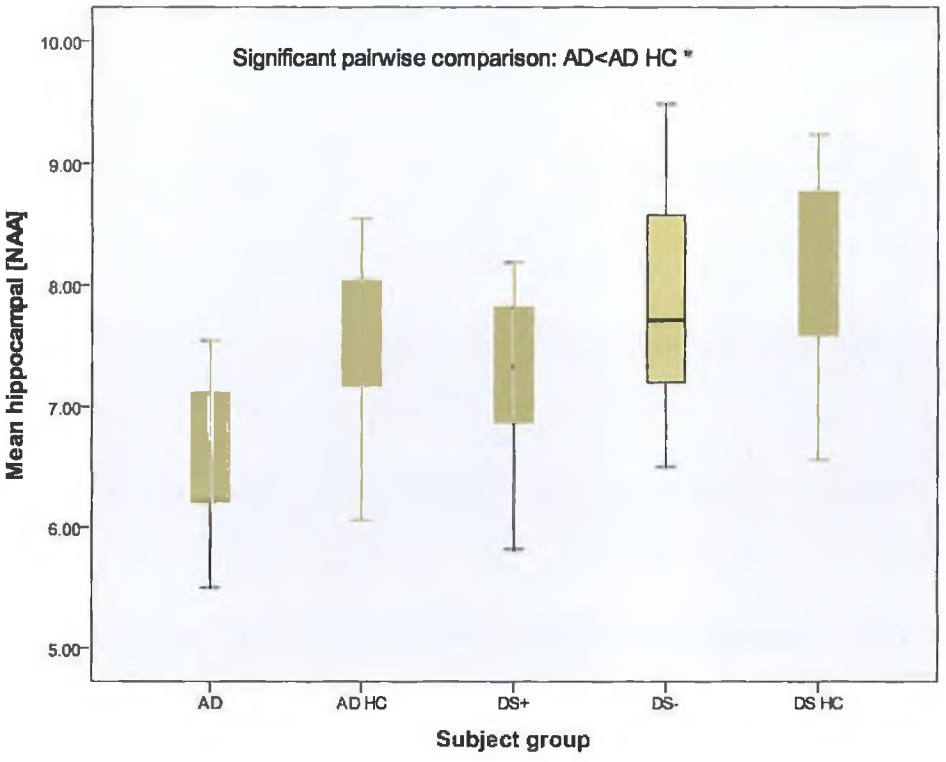


*Figure 3.15: Mean hippocampal [NAA]*

* p <0.001; Error bars represent SD

### 3.4.2 Myo-inositol [mI]

There was a significant main effect of group.

Follow-up comparisons revealed that the DS+ group had a significantly higher mI concentration than the other groups ($p<0.001$). No other follow-up comparisons were significant. Figure 3.16 shows the mean hippocampal [mI] for AD, AD HC, DS+, DS- and DS HC.

Percentage increases were at 11% for DS+ compared to DS- and 18% for DS+ compared to the age appropriate DS HC (adjusted for age and grey/white matter proportions of the MRS voxel).

Percentage increases in adjusted [mI] levels were at -17% for the AD group when compared to the age appropriate AD HC (adjusted for age and grey and white matter proportions of the MRS voxel). For comparison purposes, there was an 18% increase in adjusted [mI] levels for the DS+ group when compared to the age appropriate DS HC.

AD had a -13% increase in adjusted [mI] when compared to DS-, in comparison to an 11% increase when DS+ was compared to DS-.

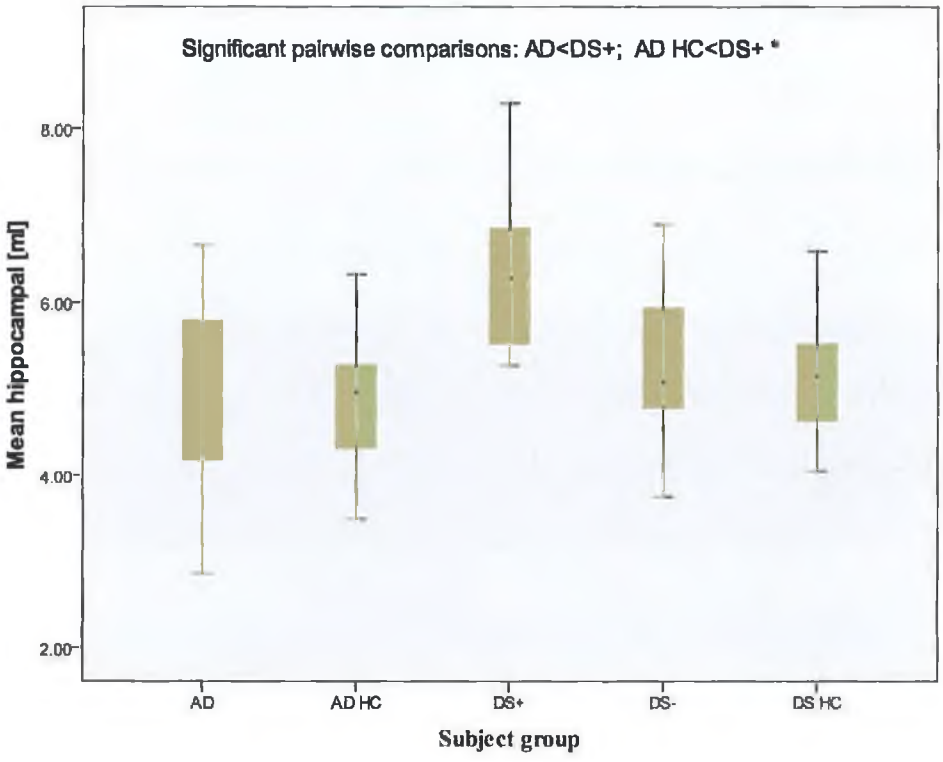


*Figure 3.16: Mean hippocampal [ml]*

* p <0.001; Error bars represent SD

### 3.4.3 Creatine and phosphocreatine [Cr+PCr]

There was no significant main effect of group or gender. No follow-up pairwise comparisons were significant.

### 3.4.4 Choline [Cho]

There was no significant main effect of group or gender. No follow-up pairwise comparisons were significant.

### 3.4.5 Relationship of cognitive ability to brain anatomy

Within the DS group, the relationship between overall cognitive ability (as measured by total CAMCOG score) and brain mI concentration was investigated. There was a significant negative correlation between mean mI concentration and overall cognitive ability ($r$ -0.463, $p < 0.001$).

| | DS+ (N=19) Mean ± SD | DS- (N=20) Mean ± SD | DS HC (N=24) Mean ± SD | AD (N=46) Mean ± SD | AD HC (N=39) Mean ± SD | F effect of group (p value) | F effect of gender (p value) | Significant pairwise comparisons |
|---|---|---|---|---|---|---|---|---|
| Age (years)* | 51.52±7.889 | 38.07±12.236 | 33.75±11.374 | 76.59±5.298 | 75.87±5.526 | 182.840 (<0.001) | NS | DS+<AD; DS+<AD HC; DS-<AD; DS-<AD; DS-<AD HC; DS HC<AD; DS HC<AD HC; DS HC<DS+ |
| Education (years) | | | | 11.13±3.215 | 1.49±2.999 | NS | NS | NS |
| Sex (M:F) | 10:9 | 31:14 | 29:14 | 22:24 | 11:28 | | | |
| MMSE* | 9.32±4.46 | 13.88±5.556 | 15.23±2.528 | 22.48±3.674 | 28.74±3.234 | 48.028 (<0.001) | NS | AD<AD HC; AD HC<DS HC; DS+<AD; DS+<AD HC; DS+<DS HC; DS+<DS-; DS-<AD; DS-<AD HC; DS HC<AD |
| CAMCOG* | 33.72±19.769 | 52.98±21.475 | 114.83±16.518 | | | 100.768 (<0.001) | NS | DS+<DS HC; DS-<DS HC |
| **MRI VOI proportions** | | | | | | | | |
| White matter* * | 0.194±0.099 | 0.196±0.053 | 0.238±0.063 | 0.195±0.067 | 0.247±0.053 | 5.678 (<0.001) | NS | AD<AD HC; DS+<DS HC |
| Grey matter* * | 0.614±0.084 | 0.67±0.039 | 0.679±0.051 | 0.615±0.082 | 0.656±0.05 | 6.977 (<0.001) | NS | AD<AD HC; DS+<AD HC; DS+<DS HC |
| CSF* * | 0.184±0.086 | 0.112±0.043 | 0.074±0.033 | 0.178±0.092 | 0.105±0.032 | 6.831 (<0.001) | NS | AD HC<AD; DS HC<DS+; DS-<DS+ |
| **Metabolite concentrations** | | | | | | | | |
| [NAA]* | 7.255±0.801 | 7.901±0.858 | 8.14±0.747 | 6.654±0.611 | 7.591±0.765 | 6.633 | 4.224 | AD<AD HC |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | (<0.001) | (0.043) | |
| [mI] * | 6.277±0.903 | 5.592±1.266 | 5.142±0.663 | 4.884±1.012 | 4.884±0.744 | 5.854 (<0.001) | NS | AD<DS+; AD HC<DS+ |
| [Cr+PCr] | 5.517±0.725 | 6.08±0.803 | 6.043±0.571 | 5.648±0.799 | 6.061±0.407 | NS | NS | NS |
| [Cho] | 1.501±0.253 | 1.623±0.264 | 1.651±0.182 | 1.392±0.273 | 1.475±1.996 | NS | NS | NS |

* p<0.001;  * *p <0.05

***Table 3.5: Magnetic resonance spectroscopy study analysis***

# Chapter 4

# Discussion

## 4.1 Overview

Dementia is a clinical condition in which the subject experiences a loss of cognitive function severe enough to interfere with their activities of daily living and social relationships. The loss of cognitive abilities resulting from the damage to neurons in certain areas of the brain is often accompanied by a deterioration in emotional control, social behaviour and motivation. The effects of the damage to the brain intensify over time and are disabling and terminal.

Alzheimer's disease is the most common form of dementia among older people, accounting for more than half of all cases. Many conditions other than Alzheimer's disease can however cause dementia, including vascular dementia which accounts for about 20% of dementia cases (Perry *et al.*, 1990), while the remainder are accounted for by a range of uncommon conditions including Pick's disease and other frontal dementias, Crutzfeldt Jacob disease, Parkinson's disease and Huntington's disease.

Alzheimer's disease is a progressive condition in which the dementia symptoms gradually worsen over a number of years. In its early stages, memory loss is mild. In

late-stage Alzheimer's disease, subjects lose the ability to converse and to respond to their environment. As with all forms of dementia, the rate of progression of the disease in people living with Alzheimer's disease varies from case to case. From the onset of symptoms, the life span of a person living with Alzheimer's disease can range anywhere from three to twenty or more years. The disease eventually leaves the individual unable to care for themselves.

In Ireland, one of the main objectives of public policy for people with dementia is to encourage and facilitate their continued living in their own homes for as long as is possible and practicable (Report of the Working Party on Services for the Elderly, 1998).

## 4.2 Early detection of dementia

Primary healthcare staff should consider referring people who show signs of mild cognitive impairment for an assessment by a memory assessment service in order to aid the early identification of dementia, because more than 50% of people with mild cognitive impairment subsequently develop dementia (NICE Clinical Guideline 42, 2006). Those undertaking health checks as part of health facilitation for people with intellectual disabilities should be aware of the increased risk of dementia in this group (NICE Clinical Guideline 42, 2006). An important example of individuals in the latter category are those suffering from Down's syndrome.

A number of potential difficulties can arise when attempting to make a diagnosis of dementia in subjects with Down's syndrome. These difficulties include the lack of a gold standard for such a diagnosis, increased level of co-morbidity and the underdevelopment of social and cognitive skills which are relatively common in subjects with Down's syndrome (Deb & Braganza, 1999). Furthermore, the expression of Alzheimer's disease in subjects with Down's syndrome can differ when these individuals are compared to the general population (Nieuwenhuis-Mark, 2009). People with Down's syndrome may not present their symptoms verbally because of their impaired communication skills. In fact, carers might be more likely to highlight a change than would the person with Down's syndrome.

Memory assessment services that identify people with mild cognitive impairment (including those without memory impairment, which may be absent in the earlier stages of non-Alzheimer's dementias) should be offered follow-up to monitor the

cognitive decline and other signs of possible dementia in order to plan care at an early stage (NICE Clinical Guideline 42, 2006).

The diagnosis of Alzheimer's disease continues to be based almost exclusively on clinical criteria, although neuroimaging is considered in many diagnostic algorithms. Despite the prevalence of Alzheimer's disease, the current treatment options remain limited for sufferers. There is therefore a great demand to enable timely detection and monitoring of dementia in its earliest stages of the condition, particularly in presymptomatic, genetically at-risk individuals, so that new putative treatment strategies can be tested.

## 4.3 Neuroimaging of dementia

Although screening neuropsychological tests are necessary to recognise and monitor subjects at risk for developing dementia or those with possible existing dementia, no definite accurate cognitive marker of early Alzheimer's disease has been identified (Chen *et al.*, 2000). The measurement of tau protein and amyloid Aβ42 in cerebrospinal fluid has some potential in the diagnosis of probable Alzheimer's disease. These investigations are however invasive in nature and have received only a minor degree of attention (Boss, 2000). Whether used alone or in combination with tests such as neuropsychological assessment (Laakso *et al.*, 2000), other approaches such as neuroimaging should therefore be considered.

Johnson *et al.* (2006) used fMRI techniques to identify early biological markers of Alzheimer's disease. The study undertaken by Johnson *et al.* (2006) involved multi-racial middle aged subjects who were comprised of those who had at least one parent with Alzheimer's disease and those who had no family history of dementia. Those subjects who did not have a family history of dementia demonstrated greater hippocampal activity on fMRI scans and had more localised brain stimulation than those subjects who had one or more demented parents. Subjects unaware of their own mental state, an early marker of dementia, showed less fMRI activity in the posterior corpus callosum and prefrontal cortices than those with mental state awareness. Significant differences were not detected among subjects of different ethnicity.

Sophisticated imaging techniques are required to characterise the complex dynamic neuro-anatomical changes that occur over time in health and disease. With the advent

of potential therapies for the treatment of degenerative dementias, imaging strategies need to enable early diagnosis and facilitate monitoring of disease progression in treatment trials.

In vivo brain structural imaging has an established role in the evaluation and monitoring of neuro-anatomical changes in Alzheimer's disease, acting as a surrogate marker for the underlying histopathological changes and, by inference, disease progression.

Structural imaging based on magnetic resonance is an integral part of the clinical assessment of patients with suspected Alzheimer's dementia. Prospective data on the natural history of the change in structural markers from preclinical to overt stages of Alzheimer disease are radically changing how the disease is conceptualised and will influence its future diagnosis and treatment.

When assessing a demented subject, structural neuroimaging is the most powerful investigation for excluding other pathologies such as tumour, hydrocephalus and multiple vascular lesions (Scheltens *et al.*, 1999; Frisoni *et al.*, 2001) and is recommended practice (Knopman *et al.*, 2001). Magnetic resonance imaging is the preferred modality to assist with the early diagnosis of dementia and to detect subcortical vascular changes, although computed tomography scanning could be used (NICE Clinical Guideline 42, 2006).

Neuroimaging studies using magnetic resonance imaging have shown that the brain experiences atrophy with increasing age. This age-related atrophy of the grey matter

is associated with an increase in ventricle size (Albert *et al.*, 1984; Jernigan *et al.*, 1991; Coffey *et al.*, 1992). It is less clear whether the white matter compartment declines globally with age, although it has been suggested that cerebral white matter volume appears to remain relatively stable until age 70 years, after which the decline is rapid (Jernigan *et al.*, 2001).

Although Alzheimer's disease is not the only cause of atrophy of the medial temporal lobe (Jobst *et al.*, 1992), it is likely to be the commonest cause of such atrophy in the elderly population. Screening for such atrophy could therefore be used to estimate the prevalence of Alzheimer's disease in different populations. Neuroimaging has dramatically changed our ability to accurately diagnose dementia. New neuroimaging methods facilitate the diagnosis of most of the neurodegenerative conditions after symptom onset and show promise for diagnosis even in very early or presymptomatic phases of some diseases.

Magnetic resonance volumetry can distinguish Alzheimer's disease subjects from controls with a sensitivity and specificity of 80% across studies (Minati *et al.*, 2009). The volume of the hippocampus has been reported to be reduced by approximately 10% in early Alzheimer's disease, by 20-30% in mild Alzheimer's disease and by more than 30% in moderate Alzheimer's disease (Minati *et al.*, 2009). Volumetry also reveals differences in the annual rate of hippocampal atrophy of between 2-6% for subjects with Alzheimer's disease, compared to less than 2% for controls, and in the rate of entorhinal atrophy of approximately 8% in subjects with Alzheimer's disease (Lehericy *et al.*, 2007). Serial neuroimaging may serve to predict which subjects with mild cognitive impairment will convert to Alzheimer's disease (Petersen *et al.*, 2005).

Class II evidence has been replicated to support volumetric analyses of the entorhinal cortex and hippocampus to identify those subjects with mild cognitive impairment who are most likely to progress to Alzheimer's disease within several years (Killiany *et al.*, 2002; Rusinek *et al.*, 2003; Jack *et al.*, 2005).

Structural neuroimaging has also shown promise in monitoring the progression of Alzheimer's disease in clinical trials, especially if the morphometry is combined with neuropsychological testing (Zakzanis, 1998; Frisoni *et al.*, 2003; Cardenas *et al.*, 2003; Zamrini *et al.*, 2004). Neuroimaging may therefore serve as a valuable instrument to monitor the effectiveness of therapies which are designed to slow or arrest the neurodegenerative process of dementia.

## 4.4 Magnetic resonance imaging to compare subjects with Down's syndrome and those with Alzheimer's disease in the general population

### 4.4.1 Down's syndrome

Subjects with Down's syndrome are at an increased risk for dementia, thought to be of the Alzheimer's disease type (Wisniewski *et al.*, 1985; Oliver & Holland, 1986; Lott & Head, 2001). The Down's syndrome model of Alzheimer's disease is useful for research because middle aged individuals can be identified prior to any clinical signs of dementia and studied longitudinally with an increased probability of conversion. The highest prevalence of dementia in a study of 506 individuals with Down's syndrome aged 45-77 years was shown to be 32.1% in the 55-59 year age group, 17.7% in the 50-54 year group and 8.9% in 45-49 year olds (Coppus *et al.*, 2006).

The hippocampal volumes in demented subjects with Down's syndrome in this study were disproportionably smaller when compared to age-matched healthy controls. This is in agreement with previous neuropathological (Wisniewski *et al.*, 1985) and neuroimaging studies of subjects with Down's syndrome (Jernigan *et al.*, 1993; Kesslak *et al.*, 1994; Raz *et al.*, 1995; Pearlson *et al.*, 1998; Alyward *et al.*, 1999) and a number of magnetic resonance studies of Alzheimer's disease subjects in the general population (Double *et al.*, 1996; Karas *et al.*, 2003; Pennanen *et al.*, 2004). Reduced hippocampal volume is not a feature of all people with an intellectual disability. In subjects with fragile X syndrome (Hessl *et al.*, 2004) and autism (Schumann *et al.*,

2004) for example, corrected hippocampal volume is reported to be significantly increased compared to healthy controls. Reduced hippocampal volume in the brains of subjects with Down's syndrome does not appear to simply reflect a non-specific effect of an intellectual disability.

Raz *et al.* (1995) examined neuroanatomic abnormalities in adults with Down's syndrome and revealed that Down's syndrome subjects had substantially smaller hippocampal formations compared to sex-matched healthy control subjects, a finding that was corroborated by others (Pinter *et al.*, 2001; Krasuski *et al.*, 2002; Teipel *et al.*, 2003). In a study examining both demented and non-demented Down's syndrome subjects, all Down's syndrome subjects revealed significantly smaller hippocampi than controls (Aylward *et al.*, 1999). Non-demented Down's syndrome adults have an age-related decrease of hippocampus volume, which is not reported in age-matched healthy comparison subjects (Teipel *et al.*, 2003).

Post-mortem studies have reported that adults with Down's syndrome have prominent neuropathology in the medial temporal lobe structures in the early stages of Alzheimer's disease (Ball *et al.*, 1986; Mann & Esiri, 1989; Hof *et al.*, 1995; Hyman *et al.*, 1995). In the current study, the volumetric findings in subjects with Down's syndrome were consistent with an Alzheimer's disease pattern of atrophy, with a reduction in the volume of the hippocampus. This result supports the finding that the hippocampus is one of the brain regions most severely affected by amyloid plaques and neurofibrillary plaques in Down's syndrome (Hoff *et al.*, 1995). These results suggest that a reduction in hippocampal volume may provide a useful tool to assist the diagnosis of dementia in subjects with Down's dementia, as has been proposed for

subjects with Alzheimer's disease in the general population (Laakso *et al.*, 1995; Yamagushi *et al.*, 2002).

### 4.4.2 Alzheimer's disease in the general population

The results of this study showed that the volume of the temporal lobe was reduced in subjects with Alzheimer's disease in the general population compared to age-matched healthy controls. This finding is consistent with those of previous magnetic resonance imaging volumetric studies (Kesslack *et al.*, 1991; Pearlson *et al.*, 1992; Jack *et al.*, 1992; Erkinjuntti *et al.*, 1993; Cuenod *et al.*, 1993; Killiany *et al.*, 1993; Convit *et al.*, 1993; Lehericy *et al.*, 1994). Jack *et al.* (2002) found smaller antemortem hippocampal volumes in Alzheimer's disease compared to non-demented subjects. The findings of the study by Jack *et al.* (2002) identified that atrophy of the hippocampus was not specific to Alzheimer's disease, occurring also in other forms of dementia. This finding was previously stated by Laakso *et al.* (1995) and Riekkinen *et al.* (1998). Gosche *et al.* (2002) found post-mortem hippocampal volume on magnetic resonance imaging was a better predictor of Alzheimer's disease neuropathology than clinical diagnosis or measures of cognition.

The medial temporal lobe plays an important role in the storage of new information (Squire & Zola-Morgan, 1991; Rombouts *et al.*, 1997). Atrophy of the medial temporal lobe may therefore explain why memory dysfunction is an early symptom of Alzheimer's disease (Storandt & Hill, 1989; Peterson *et al.*, 1994). Consistent with this, subjects with memory impairment who do not meet the criteria for dementia have

an increased risk of subsequent Alzheimer's disease (Flicker *et al.*, 1991; Linn *et al.*, 1995; Tierney *et al.*, 1996; Bowen *et al.*, 1997). In the same way, atrophy of the hippocampus increases the risk for subsequent Alzheimer's disease in elderly non-demented individuals (de Leon *et al.*, 1993; Kave *et al.*, 1997) and in asymptomatic individuals at risk for autosomal dominant Alzheimer's disease (Fox *et al.*, 1996).

Barkhof *et al.* (2007) reported high medial temporal lobe atrophy scores (greater hippocampal atrophy) to be associated with significant Alzheimer's disease pathology. Burton *et al.* (2007) found medial temporal lobe atrophy to be a highly accurate diagnostic marker for autopsy confirmed Alzheimer's disease (sensitivity 91% and a specificity of 94%) using receiver operator curve analysis, compared with lewy body dementia and vascular cognitive impairment. Medial temporal lobe atrophy on magnetic resonance imaging has a robust discriminatory power for distinguishing Alzheimer's disease from dementia with lewy bodies and vascular cognitive impairment in pathologically confirmed cases (Burton *et al.*, 2009).

The first volumetric magnetic resonance imaging study of Alzheimer's disease published in 1988 (Seab *et al.*, 1988) described a 40% reduction in the volume of the hippocampus of subjects with Alzheimer's disease compared to healthy controls. Subsequent studies have similarly reported atrophy of the hippocampal and parahippocampal formation in Alzheimer's disease, ranging from 20-52% (Mega *et al.*, 2000) and already present at the first stages of Alzheimer's disease (Fox & Rossor, 1999b; Celsis, 2000). The results of the current study showed that within Down's syndrome individuals, the reduction in the volume of the hippocampus between demented subjects and non-demented subjects was similar to that within

Alzheimer's disease cases and controls from the general population (respectively 19% and 17%)

The results of neuroimaging which demonstrates atrophy of the hippocampus has the potential to provide useful diagnostic information which could be used to distinguish subjects with probable Alzheimer's disease from healthy elderly subjects (Scheltens, 1999).

The current study in pathologically confirmed cases provides further support to the already established body of literature that shows atrophy of the hippocampus and temporal lobe to be significant factors which distinguishes subjects with Alzheimer's disease from healthy controls.

The Alzheimer's disease process preferentially affects large neocortical cells with corticocortical connections (Brun & Englund *et al.*, 1981; Pearson *et al.*, 1985; Lewis *et al.*, 1987). Death of these large cells and the subsequent axonal degeneration and loss of cerebral white matter that ensues (De la Monte, 1989) may be the pathophysiological explanation for increases in ventricular volume related to the Alzheimer's disease process in these individuals.

### 4.4.3 Subjects with Down's syndrome and those with Alzheimer's disease in the general population

This study compared for the first time, differences in brain anatomy associated with a diagnosis of Alzheimer's disease in the general population and dementia in Down's syndrome. The results showed that demented individuals, as compared to their respective non-demented counterparts, had a reduction in the volume of whole brain, temporal lobe and hippocampus; in addition to an elevation in lateral ventricle volume.

The initial findings were however potentially confounded by significant between-group differences in brain size, age and gender. To overcome the potential confounder of brain size, all volumes were corrected for total cranial volume. Age was significantly different between groups. This is a confounder because age-related reductions in hippocampal volume in non-demented subjects with Down's syndrome have been reported in previous volumetric magnetic resonance imaging studies of brain aging (Murphy *et al.*, 1993b; Kesslak *et al.*, 1994). However, this was expected as it is very difficult to 'age-match' equivalent older populations of Down's syndrome and non-Down's syndrome individuals. While ideally all study groups would be equivalent in age, including Alzheimer's disease and demented subjects with Down's syndrome, life expectancy estimates suggest that only 14% of the Down's syndrome population (demented or otherwise) reach the age of 68 years (Coppus *et al.*, 2006), while the age of onset for non-familial Alzheimer's disease in the general population is 65 years and over. Therefore obtaining 70-85 year old age-matched Down's syndrome samples for comparison to Alzheimer's disease in the general population is

almost impossible. Nevertheless, age differences were corrected in the analyses in this study. Age, gender and total cranial volume were used as covariates in the analyses.

Following normalisation and correction for confounders, it was found that both the Alzheimer's disease group in the general population and demented subjects with Down's syndrome had a significant reduction in hippocampal volume when compared to their comparison control groups. The Alzheimer's disease group also showed a significant reduction in temporal lobe volume and a significant increase in lateral ventricle volume compared to its age-matched control group. Hypothesis 1 which stated that subjects with dementia have a significant reduction in the volume of the hippocampus, temporal lobe and whole brain and an increase in the volume of the lateral ventricles compared to their non-demented controls, was therefore proven in this study.

This phase of the research was a cross-sectional study and clinical rather than post-mortem criteria were used to identify subjects with Alzheimer's disease and demented subjects with Down's syndrome. Hence, it is not possible to be certain that all of the cases of dementia under investigation had Alzheimer's disease, as this can only be definitively addressed at autopsy. Nevertheless, all the demented individuals from both groups (Down's syndrome and Alzheimer's disease in the general population) were diagnosed using standardised instruments and individuals with detectable cerebrovascular disease were excluded. Therefore the group differences found in brain anatomy between demented Down's syndrome individuals and those in the general population most probably reflect Alzheimer's disease-type neuropathology.

Although amyloid plaques and neurofibrillary tangles are reliable semi-quantitative markers for the presence of Alzheimer's disease pathology, there is no compelling evidence that they, by themselves, cause dementia (Mann *et al.*, 1990). Factors such as education, adult-life occupational work complexity, in addition to late life social network and leisure activities may contribute to the cognitive reserve and necessitate more severe pathological changes to produce functional clinical impairment (Stern, 2006). These factors may therefore significantly reduce the risk of dementia, or delay the manifestations of dementia symptoms by using cognitive processing or compensatory approaches that enable these individuals to cope better with brain damage. The most positive findings have been recorded for complex leisure activities which involve a physical, mental and social component (Karp *et al.*, 2006).

A higher level of cognitive functioning has been shown to be associated with fewer cases of dementia in people with Down's syndrome, and the level of cognitive functioning appears to be associated with environmental factors such as level of education and employment (Temple *et al.*, 2001).

### 4.4.4 Relationship of cognitive ability to brain anatomy

The results of this study showed that atrophy of the hippocampus and temporal lobe were correlated with cognitive decline. In the Alzheimer's disease population, there was a positive correlation between MMSE and the corrected hippocampal volume and between MMSE and the corrected temporal lobe volume. The correlation between

MMSE and volume reduction in these critical areas suggests that the function of the hippocampus and temporal lobe is compromised when the volume is reduced. One may speculate that severe medial temporal lobe atrophy is associated with faster cognitive decline. This is line with the finding that a small volume of the hippocampus at baseline (Golomb *et al.*, 1996) is associated with a decrease in cognitive scores during follow-up. Hypothesis 2 which stated that there is a significant correlation between atrophy of the hippocampus and temporal lobe, and cognitive decline, was therefore proven in this study.

Some previous studies have shown that performance on the MMSE was directly correlated with hippocampal volume (Laasko *et al.*, 1995). These findings confirm fundamental differences in the patterns of volume loss in aging and Alzheimer's disease, and support hippocampal and temporal lobe degeneration as a basis for cognitive decline in Alzheimer's disease.

Although bilateral lesions restricted to the hippocampi produce memory impairment in animals (Squire & Zola-Morgan, 1991; Alvarez *et al.*, 1995) and in humans (Zola-Morgan *et al*, 1986), the deficits may be considered to be more extensive. Damage to the hippocampus may be an indispensable condition for the occurrence of memory deficits in subjects with Alzheimer's disease. The damage to the amygdala proper, its surrounding cortices and the subiculum, exacerbates further the memory impairment following the initial damage to the hippocampus (Mori *et al.*, 1997).

## 4.5 Automated volume and thickness measurements

### 4.5.1 Overview

Much attention has focused on volumetric MRI studies to investigate changes occurring early in Alzheimer's disease. Manual methods are typically Region of Interest (ROI) studies which tend to focus on a few specific brain regions which are well established as being affected in Alzheimer's disease such as in the entorhinal cortex or the hippocampus (Van Hoesen *et al.,* 1995; De Leon *et al.,* 1997; Mori *et al.,* 1997; Krasuski *et al.,* 1998; De Toledo-Morell *et al.,* 2000). ROI studies are often used when the investigators have *a priori* hypotheses and therefore, assessments are confined to a limited set of brain regions. These methodologies are in concept simple and are carried out for instance by manually tracing the structures or regions-of-interest on conventional MRI or alternatively, via semi-automated techniques such as stereology where a 3-D grid of fixed dimensions is placed on the entire brain and subsequently the volumes of structures of interest are calculated by the manual marking of pixels falling within each 2-D slice of the structure of interest by a rater. The volume of the structure of interest which corresponds to the total number of marked pixels is then automatically calculated by computer software.

Automatic techniques have been developed to study more widespread brain volume and thickness measures (Fischl *et al.,* 1999; Dale *et al.,* 1999; Fischl & Dale, 2000). Studies of cortical thickness have demonstrated thinning in distributed association areas, suggesting that regional atrophy can be detected across widespread cortical

regions (Lerch *et al.* 2005; Du *et al.* 2007). Dickerson *et al.* (2009) demonstrated abnormal cortical anatomy in Alzheimer's disease, which paralleled known regional vulnerability to Alzheimer's disease neuropathology.

### 4.5.2 Automated volume measures

This study compared for the first time, global differences in brain volumes and thickness measures associated with a diagnosis of Alzheimer's disease in the general population and Down's syndrome. Previous magnetic resonance imaging studies of dementia have tended to focus on the limbic system (Callen *et al.* 2001). These studies were limited to either Alzheimer's disease in the general population or to Down's syndrome.

Most of the uncorrected brain volumes were significantly smaller in subjects with Alzheimer's disease and demented subjects with Down's syndrome compared to their respective non-demented controls. However, these initial findings were potentially confounded by significant between-group differences in brain size, age and gender. To overcome the potential confounder of brain size, all volumes were normalised to total cranial volume. The normalisation to total cranial volume represented the premorbid brain size. Age was significantly different between groups. There were also more female Alzheimer's disease subjects and aged-matched healthy controls; and more male non-demented subjects with Down's syndrome and Down's syndrome aged-matched healthy controls, than expected by chance. Age and gender were therefore added as covariates in the analyses.

Clinical rather than post-mortem criteria were used to identify subjects with Alzheimer's disease and demented subjects with Down's syndrome. Demented individuals from both groups were recruited using standardised instruments. Subjects with detectable physical health difficulties were excluded. Therefore the group differences found in brain anatomy most probably reflect the Alzheimer's disease-type neuropathology rather than other types of neuropathology.

The hippocampus and amygdala volumes were reduced in subjects with Alzheimer's disease and demented subjects with Down's syndrome compared to their respective non-demented controls. This finding is consistent with previous reports that the hippocampus and amygdala are affected in dementia (Kesslak *et al.*, 1994; Double *et al.*, 1996; Prasher *et al.*, 1998; Pearlson *et al.*, 1998; Aylward *et al.*, 1999; Pennanen *et al.*, 2004). In the Alzheimer's disease group, both the left and right normalised amygdala volumes were similarly reduced by approximately 30% compared to their non-demented controls. This is consistent with previous studies which have reported between 14-44% reduction (Cuenod *et al.*, 1993; Laakso *et al.*, 1995; Witwell *et al.*, 2005).

Normalised anterior, mid-anterior, central, posterior and mid-posterior corpus callosum volumes were reduced in Alzheimer's disease compared to its non-demented control group. Corpus callosum atrophy has been suggested as a marker for neuronal loss in Alzheimer's disease. Several MRI studies have reported corpus callosum atrophy in Alzheimer's disease that was correlated with PET and EEG measures of neocortical dysfunction (Yamauchi *et al.*, 1993; Janowsky *et al.*, 1996; Teipel *et al.*, 1998, 1999; Hampel *et al.*, 1998, 2002).

The normalised volume of the left putamen was significantly reduced in the Alzheimer's disease group compared to its non-demented control group. The putamen has been previously correlated with Alzheimer's disease since amyloid deposits are present early in the disease process (Braak & Braak, 1990).

Progressive cerebral atrophy and an increase in third ventricle size observed in older Down's syndrome subjects have been associated with demented subjects with Down's syndrome (Schapiro *et al.*, 1989; Le May & Alvarez, 1990) and Alzheimer's disease in the general population (Silbert *et al.*, 2003). The third ventricle enlargement in Alzheimer's disease and in demented subjects with Down's syndrome, compared to their respective non-demented control groups, may reflect cellular neuropathological changes associated with the early and inevitable development of plaques and tangles and possibly the onset of dementia. The lateral and inferior lateral ventricle volumes were also increased in Alzheimer's disease and in demented subjects with Down's syndrome compared to their respective non-demented controls.

This study showed that compared to demented subjects with Down's syndrome, subjects with Alzheimer's disease had significantly reduced corrected volumes of the amygdala, left putamen, right cerebral cortex and corpus callosum (anterior, mid-anterior, posterior components and mid-posterior components), and significantly greater corrected volumes of the brain stem, cerebellar cortex and cerebellar white matter. These differences between demented subjects with Down's syndrome and subjects with Alzheimer's disease may serve as discriminating factors between these conditions.

### 4.5.3 Automated thickness measures

Techniques which incorporate automated surface reconstruction, transformation and high-resolution inter-subject alignment procedures have been developed to enable the measurement of cortical thickness (Fischl *et al.*, 1999; Dale *et al.*, 1999; Fischl & Dale, 2000). When subjects with Alzheimer's disease and demented subjects with Down's syndrome were compared to their age-matched healthy controls, a significant reduction for Alzheimer's disease subjects was found in the caudal middle frontal gyrus, cuneus cortex, entorhinal cortex, frontal operculum, fusiform gyrus, inferior parietal cortex, inferior temporal gyrus, isthmus of cingulate cortex, lateral occipital cortex, lingual gyrus, medial orbital frontal gyrus, middle temporal gyrus, orbital operculum, paracentral sulcus, parahippocampal gyrus, pericalcarine cortex, postcentral gyrus, posterior cingulate cortex, precentral gyrus, precuneus cortex, rostral middle frontal gyrus, superior frontal gyrus, superior frontal gyrus, superior pariental cortex, superior temporal gyrus and supramarginal gyrus. In contrast, demented subjects with Down's syndrome showed increased thickness of the lingual gyrus and medial orbital frontal gyrus, when compared to age-matched healthy controls. The differences between the findings for Alzheimer's disease and Down's syndrome and their respective control groups signified variations in brain pathology between the forms of dementia in both of these conditions.

The results of this study showed a reduction in thickness measures in multiple areas of the brain in subjects with Alzheimer's disease compared to its non-demented control group. The characteristic pattern of cortical thinning in Alzheimer's disease in this study replicates previous findings (Lerch *et al.*, 2005; Du *et al.*, 2007) and is

consistent with the pattern of tissue loss reported by histopathological and volumetric MRI studies (Braak & Braak, 1995, 1998; Baron *et al.*, 2001).

The greatest reductions in Alzheimer's disease compared to its non-demented control group were detected for the entorhinal cortex, parahippocampal gyrus and the isthmus of cingulate cortex. Cortical thickness analysis may serve as a surrogate marker for the neuronal loss that accompanies the histopathological changes in the cortex which occur in Alzheimer's disease and in demented subjects with Down's syndrome.

This is the first study to my knowledge which compared thickness measures in Alzheimer's disease with those in Down's syndrome. This study showed that compared to demented subjects with Down's syndrome, subjects with Alzheimer's disease had significantly reduced thickness of the caudal middle frontal gyrus, cuneus cortex, frontal operculum, fusiform gyrus, inferior parietal cortex, isthmus of cingulate cortex, lateral occipital cortex, lateral occipital frontal cortex, lingual gyrus, medial orbital frontal gyrus, orbital operculum, parahippocampal gyrus and pericalcarine cortex. The reduced thickness measures in Alzheimer's disease relative to Down's syndrome may signify that Alzheimer's disease is a more severe form of dementia than is found in subjects with Down's syndrome.

Hypothesis 3 which stated that significant differences for more global volume and thickness measures exist between demented and non-demented subjects, and enables the distinction of subjects with Alzheimer's disease from demented subjects with Down's syndrome, was therefore proven in this study.

## 4.6 Magnetic resonance imaging of subjects with Alzheimer's disease, mild cognitive impairment and Alzheimer's disease healthy controls, scanned at baseline and re-scanned at 12 months

Since it is impossible to accurately predict which subjects will eventually develop Alzheimer's disease, longitudinal data on a sample of the population could be collected in order to undertake analysis of the initial characteristics of those individuals who eventually convert to dementia. A study of such nature would require a large number of subjects in order to have a sample of a sufficient size of converters for valid statistical analysis. Furthermore, such a large scale study involving neuroimaging would be cumbersome and expensive to implement. It therefore appears more appropriate to recruit at-risk subjects who are at a higher risk of developing Alzheimer's disease.

Longitudinal studies of Alzheimer's disease offer some distinct advantages over cross-sectional studies, not only because dynamic changes can be monitored, but also because subjects can be used as their own controls. In this way, subtle pathological changes within individuals are not masked by wide physiological variability. A clear distinction has been reported between the rates of atrophy in subjects with Alzheimer's disease compared to controls (Fox *et al.*, 1996, 1997, 1999a, 2000, 2001; Scahill *et al.*, 2002). Importantly, quantifiable rates of atrophy have been reported in presymptomatic patients at risk for Alzheimer's disease.

The results of this study showed that there was significantly greater hippocampal and temporal lobe atrophy in the Alzheimer's disease group than in those with mild cognitive impairment, and in the Alzheimer's disease group compared to the age-matched healthy controls at both $T_1$ and $T_2$. The volume of the lateral ventricles was greater in subjects with Alzheimer's disease than in age-matched healthy controls at both $T_1$ and $T_2$.

The mean hippocampal and temporal lobe volumes were reduced at $T_2$ compared to $T_1$. These results suggest the progression of typical Alzheimer's disease brain pathology. The volumes of the hippocampus and temporal lobes of subjects with mild cognitive impairment were shown to be smaller than normal controls and greater than subjects with Alzheimer's disease. Hypothesis 4 which stated, in a longitudinal study, when compared to age matched healthy controls, subjects with Alzheimer's disease have a significant reduction in the volume of the hippocampus and temporal lobe, and an increase in the volume of the lateral ventricles at baseline and when re-scanned at 12 months, and subjects with mild cognitive impairment have findings intermediate between those of Alzheimer's disease and age matched healthy controls, was therefore proven in this study.

Serial magnetic resonance imaging studies have demonstrated that atrophy rates predict the conversion of mild cognitive impairment and normal cognitive function to Alzheimer's disease (Yavus *et al.*, 2007). Detecting hippocampal atrophy by neuroimaging in mild cognitive impairment may help in differential diagnosis, but as it is not a specific finding, the main contribution of magnetic resonance imaging is in

the identification of the high risk groups who are at an increased risk for progression to Alzheimer's disease (Jack *et al.*, 2005).

Both progressive cognitive decline, assessed from serial neuropsychometric assessments, and the rate of cerebral atrophy calculated from serially acquired volumetric MRI scans (Fox *et al.*, 1996; Smith & Jobst, 1996; Jack *et al.*, 2003), have been proposed and utilised as biomarkers of disease progression. Previous cross-sectional studies in Alzheimer's disease have demonstrated relationships between cognitive deficits and cortical atrophy at post-mortem (Mouton *et al.*, 1998) and with MRI measures of whole brain (Murphy *et al.*, 1993b) and hippocampal volume (Jack *et al.*, 1997).

There was a positive correlation between MMSE and both hippocampus and temporal lobe volumes corrected for total cranial volume. In previous longitudinal studies, the rate of progression of hippocampal atrophy in serial magnetic resonance and the progression of dementia was found to be correlated (Jack *et al.*, 2004). The findings of this study show that as the severity of cognitive decline increases, the severity of hippocampal atrophy increases as well. As a result, it can be stated that hippocampal volumetry may be helpful in assisting the diagnosis and the grading of cognitive impairment.

## 4.7 Magnetic resonance spectroscopy

The hippocampal concentration of N-acetyl aspartate [NAA] was significantly reduced in subjects with Alzheimer's disease compared to age appropriate healthy controls. Myo-inositol [mI] was significantly increased in subjects with Down's syndrome compared to those with Alzheimer's disease and Alzheimer's disease healthy controls. Myo-inositol concentration was significantly negatively correlated with overall cognitive ability, as measured by the CAMCOG total score.

It has been reported that glia contain elevated concentrations of mI. Loss of neurons with subsequent gliosis could hypothetically cause the increase in mI observed in demented subjects with Down's syndrome. Elevation of mI has also been reported in frontotemporal dementia. This suggests that an elevation of mI is not specific for dementia but rather a marker for gliosis (Shonk *et al.*, 1995; Ernst *et al.*, 1997). It has also been suggested that alterations in cellular detoxification pathways and in the inositol triphosphate intracellular second messenger cycle may account for increases in this metabolite (Valenzuela & Sachdev, 2001).

Myo-inositol may result in a loss of neuronal functioning and eventual neuronal death since mI influences neuronal development, survival, osmolarity and membrane survival. In addition, mI is a precursor for key phospholipids involved in calcium concentrations in the brain and so may indirectly effect $Ca^{2+}$ homeostasis (Yao *et al.*, 2000); a process already implicated in the neurotoxic cascade of Alzheimer's disease (Emilsson *et al.*, 2006) and Down's syndrome (Schuchmann *et al.*, 1998). mI may initiate a cascade of secondary changes at different levels of the signal transduction

process and gene expression in the central nervous system. There are therefore a number of potential mechanisms in which increased mI concentration may be causally linked to neuronal dysfunction. mI may thus independently increase the risk for dementia. It is however possible that there is a 'double hit' of reduced cognitive reserve with supra-added Down's syndrome specific risk factors (e.g. mI and trisomy of the APP gene) which act as a 'tipping point' into dementia in this vulnerable population.

In addition to the suggestion that mI is a marker of gliosis in dementia, one study reported that the concentration of phosphatidylinositol was significantly lower in Alzheimer's disease (Stokes & Hawthorne, 1987). These findings were not however replicated in another study (Nitsch *et al.*, 1992). Defects in postsynaptic intracellular signal transduction have been reported in Alzheimer's disease (Young *et al.*, 1998). It is possible that these coexist with abnormalities in intracellular systems for inositol homeostasis.

Huang *et al.* (1999) reported that brain mI concentration in adults with Down's syndrome without dementia significantly increased with age. They suggested that this increase reflected a pre-dementia phase in which the neuropathological features of Alzheimer's disease were accumulating but preceded the loss of neurons.

The possibility that increased mI concentration in the Down's syndrome brain may be associated with a greater degree of intellectual disability and/or later Alzheimer's disease suggests that trials are required to determine whether a reduction in brain mI

concentration enhances the overall cognitive outcome in subjects with Down's syndrome.

The percentage reduction in NAA seen in Alzheimer's disease compared to age matched healthy controls was comparable to that in subjects with Down's syndrome compared to age matched healthy controls but slightly less than double that of subjects with Down's syndrome compared to non-demented subjects with Down's syndrome. The percentage increase in mI in demented subjects with Down's syndrome when compared to Alzheimer's disease and Alzheimer's disease healthy controls was double that seen in demented subjects with Down's syndrome compared to non-demented subjects with Down's syndrome. Therefore significant reductions in NAA in Alzheimer's disease combined with significant elevations in mI in demented subjects with Down's syndrome suggests that the biological associates of dementia in Alzheimer's disease and demented subjects with Down's syndrome are different from that of the general population.

N-acetyl aspartate is found in neurons, neuroglial precursor cells and immature oligodendrocytes. NAA is considered to be a neuronal density marker and is involved in several biochemical processes, e.g. lipid synthesis, aspartate metabolism and osmotic cell regulation. There is evidence to suggest that NAA is involved in myelination. Disturbances in the level of NAA have been detected in such conditions as multiple sclerosis, amyotrophic lateral sclerosis, epilepsy, neurodegenerative diseases and brain ischaemia (Cendes *et al.*, 1997; Demougeot *et al.*, 2004).

The reduction in NAA in Alzheimer's disease could be a marker of decreased cognitive functioning in Alzheimer's disease, reflective of a progressive loss of neuronal activity and may indicate a neurodegenerative process. Relative to healthy controls, a reduced concentration of NAA has been found in the medial temporal lobe (21% difference) and in the cortex of the parietal lobe (13% difference) of individuals with Alzheimer's disease as well as a smaller hippocampus (29% difference), without significant differences between both sides (Schuff *et al.*, 2002).

Hypothesis 5 which stated that significant metabolite differences exist between demented and non-demented subjects was proven in this study by means of the differences which were reported in NAA and mI levels.

No significant pairwise comparisons were found for choline, which is considered to be a marker of degradation products of myelin. The role of choline in the development of dementia is not completely clear and there are differing opinions regarding its level in subjects with cognitive impairment. Some researchers, including Du *et al.* (2001), Kantarci *et al.* (2002) and Chantal *et al.* (2002) have reported an age-progressive increase in the level of choline compounds with increased concentrations in Alzheimer's disease. Other researchers have reported reduced levels of choline compounds in Alzheimer's disease and in demented subjects with Down's syndrome such as Shonk *et al.* (1995), Berry *et al.* (1999), Huang *et al.* (1999), Beacher *et al.* (2005) and Smigielska-Kuzia & Sobaniec (2007). The changeability of choline concentrations suggests that the differing results may reflect both brain aging itself and the ongoing degenerative disease (Smigielska-Kuzia, 2007).

There was no evidence in this study that subjects with Down's syndrome without dementia had differences from age-matched controls in the number of viable neurons or mitochondrial function as measured by NAA concentration. There was also no evidence that subjects with Down's syndrome without dementia had differences in neuronal development and survival, cellular osmolarity, membrane metabolism, signal transduction, protein C activation or amyloid deposition, as measured by mI concentration.

No differences were identified in this study between subjects with Down's syndrome without dementia and age-matched controls for choline, a marker of membrane synthesis and degradation, or for creatine plus phosphocreatine which reflects high energy phosphate metabolism. It is possible that subjects with Down's syndrome have differences in neuronal integrity that were not detected in this study, the results of which suggest that the largest detectable contribution to cognitive impairment from the metabolites measured using $^{1}$H-MRS, is derived from increased mI concentration.

Concentrations of certain amino acids have been shown to be significantly reduced in the brains of people with Alzheimer's disease but not in Down's syndrome, despite the presence of Alzheimer's disease-like neuropathological hallmarks (Seidl *et al.*, 2001). In contrast to Alzheimer's disease, a tendency towards lower GABA, glutamate and aspartate levels in the caudate nucleus of Down's syndrome has been reported (Seidl *et al.*, 2001). A significant reduction of glutamate has been described in the hippocampus (Reynolds & Warner, 1988) and the parahippocampal gyrus in subjects with Down's syndrome. The clinical relevance of these changes is

emphasised because glutamatergic dysfunction is a strong correlate of cognitive decline in dementia.

GABAergic deficits have been identified in cortical areas of Alzheimer's disease subjects, which are not or only to a much lower degree present in Down's syndrome despite an abundance of Alzheimer's disease-like neuropathology (Seidl *et al.*, 2001). These findings may be relevant to understanding the different pathogenesis of cognitive and non-cognitive (behavioural) features in Down's syndrome and Alzheimer's disease.

## 4.8 Future work

The natural evolution of structural brain changes and their relationship with non-structural markers should be further studied at the asymptomatic stage preceding mild cognitive impairment. Investigating the most accurate combination of markers for early diagnosis and progression of dementia should provide valuable additional information on the contributions to cognitive impairment of genetic and/or neurodevelopmental change. Furthermore, extensive evaluation of such markers should facilitate effective tracking of dementia and serve as an outcome measure in clinical trials.

Neuroimaging of cerebrospinal fluid markers of amyloid deposition and glucose metabolism should be further evaluated when integrated with an automated

assessment of structural markers for optimal diagnosis and monitoring of dementia, such as the rates of brain atrophy.

It is important to fully validate the generalisability of structural magnetic resonance imaging as a biomarker in clinically based cohorts in which the presence of multiple pathologies and disorders is a norm rather than an exception.

Structural imaging changes lie at the crossroads between the molecular pathology of Alzheimer's disease and the clinical and cognitive decline that follow from that pathology. Structural imaging is well placed to contribute to improved early diagnosis of Alzheimer's disease and to the search for effective treatments to slow or prevent this devastating disease. Future therapeutic approaches in the treatment of individuals with Alzheimer's disease should consider in vivo measurements of cholinesterase function by means of neuroimaging and developing preventive strategies for the condition; including Aβ immunisations and inhibitors of β- and γ-secretase.

Due to the fact that magnetic resonance imaging scanners are widely available and magnetic resonance spectroscopy enables a non-invasive detection of changes in brain structure and metabolism, there is an increasing interest in the use of magnetic resonance spectroscopy to monitor treatment effect in clinical trials of neurodegenerative disease (Loos, 2010). Magnetic resonance spectroscopy is not currently recommended for routine evaluation of dementia as the superiority to clinical criteria has not been demonstrated (Knopman *et al.*, 2001). There is therefore an important missing factor in the available literature on the efficacy of magnetic

resonance spectroscopy in clinical decision making and therapeutic choice. This area should be further explored and evaluated.

Magnetic resonance scanners operating at magnetic-field strengths higher than 1.5 T are increasingly being used because they provide higher sensitivity and spatial resolution, with 3 T (128 MHz) scanners becoming commonplace and scanners operating at 7 T (300 MHz) and above, appearing in research environments. The introduction of such scanners should improve spectral resolution and enhance the available diagnostic information on dementia by means of more accurate quantification of magnetic resonance spectroscopy metabolites such as glutamine and glutamate. Magnetic resonance spectroscopy is a promising investigational technique in ageing and dementia at this time. The potential clinical application of magnetic resonance spectroscopy in ageing and dementia, however, is growing with technical advances in the field.

A strength of this study was the large sample size of subjects with Alzheimer's disease and Down's syndrome, in which the dementia was diagnosed by means of standardised instruments. Furthermore, the author was blind to subject status for volumetric brain regions of interest which were traced as part of the analysis. A limitation of the study was the difference in age between subjects with Alzheimer's disease and Down's syndrome. While ideally all study groups would be equivalent in age, including Alzheimer's disease and Down's syndrome, life expectancy estimates suggest that only 14% of the Down's syndrome population (demented or otherwise) reach the age of 68 years (Coppus *et al.*, 2006), while the age of onset for non-familial Alzheimer's disease in the general population is 65 years and over. Therefore

obtaining 70-85 year old age-matched Down's syndrome samples for comparison to Alzheimer's disease in the general population is almost impossible. Furthermore, clinical rather than post-mortem criteria were used to identify subjects with Alzheimer's disease and demented subjects with Down's syndrome. Hence, it is not possible to be certain that all cases of had Alzheimer's disease, as this can only be definitively addressed at autopsy. Nevertheless, all the demented individuals from both groups (Alzheimer's disease and Down's syndrome) were diagnosed using standardised instruments and individuals with detectable cerebrovascular disease were excluded. Therefore the group differences found in brain anatomy between demented Down's syndrome individuals and those in the general population most probably reflect Alzheimer's disease-type neuropathology.

In summary, to my knowledge, prior to the current study, no in vivo case-control study compared the anatomy of dementia in Down's syndrome to people with Alzheimer's disease in the general population. It is hoped that the current study will add to the existing literature.

## References

Albert M, Naeser MA, Levine HL. Ventricular size in patients with presenile dementia of the Alzheiemr's type. Arch Neurol 1984; 41: 1258-1263.

Alvarez P, Zola-Morgan S. The medial temporal lobe memory system. Science 1991; 20: 1380-1386.

Aylward EH, Li Q, Habbak QR, Warren A, Pulsifer MB, Barta PE, Jerram M, Pearlson G: Basal ganglia volume in adults with Down syndrome. Psychiatry Res 1997; 74: 73-82.

Aylward EH, Qiang Li, Honeycutt NA, Warren AC, Pulsifer MB, Barta PE, Chan MD, Smith PD, Jerram M, Pearlson GD. MRI volumes of the hippocampus and amygdala in adults with Down's syndrome with and without dementia. Am J Psychiatry 1999; 156: 564-568.

Alzheimer A. On a peculiar disease of the cerebral cortex. Allg Z Psychiat 1907; 64: 146.

Alzheimer's Disease International World Alzheimer Report. Alzheimer's Disease International 2009.

Arriagada PV, Growdon JH, Hedley-Whyte ET, Hyman BT. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. Neurology 1992a; 42: 631-639.

Arriagada PV, Marzloff K, Hyman BT. Distribution of Alzheimer-pathologic changes in nondemented elderly individuals matches the pattern in Alzheimer's disease. Neurology 1992b; 42: 1681-1688.

Ball MJ, Schapiro MB, Rapoport SI. Neuropathological relationships between Down syndrome and senile dementia Alzheimer type. Neurobiology of Down syndrome, edited by Epstein C. New York, Raven Press 1986; pp 45-58.

Barkhof F, Polvikoski TM, van Straaten ECW, Kalaria RN, Sulkava R, Aronen HJ. The significance of medial temporal lobe atrophy: a post-mortem MRI study in the very old. Neurology 2007; 69: 1521-1527.

Baron JC, Chetelat G, Desgranges B. In vivo mapping of gray matter loss with voxel-based morphometry in mild Alzheimer's disease. Neuroimage 2001; 14: 298-309.

Barta PE, Dhingra L, Royall R, Schwartz E. Efficient estimates for the volume of structures identified in three-dimensional arrays of spatial data. J Neurosci Methods 1997; 75: 111-118.

Bates TE, Strangward M, Keelan J, Davey GP, Munro PM, Clark JB. Inhibition of N-acetylaspartate production: implications for 1H MRS studies in vivo. Neuroreport 1996; 7: 1397-1400.

Beacher F, Simmons A, Daly E, Prasher V, Adams C, Margallo-Lana ML, Morris R, Lovestone S, Murphy K, Murphy DGM. Hippocampus myo-inositol and cognitive ability in adults with Down syndrome. An in vivo proton magnetic resonance spectroscopy study. Arch Gen Psychiatry 2005; 62: 1360-1365.

Beacher F, Daly E, Simmons A, Prasher V, Morris R, Robinson C, Lovestone, Murphy K, Murphy DGM. Alzheimer's disease and Down's syndrome: an in vivo MRI study. Psychol Med 2009; 39: 675-684.

Becker LE, Armstrong DL, Chan F. Dendritic atrophy in children with Down's syndrome. Ann Neurol 1986; 20: 520-526.

Bendszus M, Reents W, Franke D, Mullges W, Babin-Ebell J, Koltzenburg M, Warmuth-Metz M, Solymosi L. Brain damage after coronary artery bypass grafting. Arch Neurol 2002; 59: 1090-1095.

Bennett DA, Wilson RS, Schneider JA, Evans DA, Mendes de Leon CF, Arnold SE, Barnes LL, Bienias JL. Education modifies the relation of AD pathology to level of cognitive function in older persons. Neurology 2003; 60: 1909-1915.

Berg L, McKeel DW Jr, Miller JP, Baty J, Morris JC. Neuropathological indexes of Alzheimer's disease in demented and nondemented persons aged 80 years and older. Arch Neurol 1993; 50: 349-358.

Berr C, Wancata J, Ritchie K. Prevalence of dementia in the elderly in Europe. Eur Neuropsychopharmacol 2005; 15: 463-471.

Berry GT, Wang ZJ, Dreba SF, Finucane BM, Zimmerman RA. In vivo brain myo-inositol levels in children with Down syndrome. J Pediatr 1999; 135: 94-97.

Bowen J, Teri L, Kukull W, McCormick W, McCurry S, Larson E. Progression to dementia in patients with isolated memory loss. Lancet 1997; 349: 763-765.

Birken DL, Oldendorf WH. *N*-acetyl-L-aspartic acid: a literature review of a compound prominent in $^{1}$H-NMR spectroscopic studies of brain. Neurosci Biobehav Rev 1989; 13: 23-31.

Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. Br J Psychiatry 1968; 114: 797-811.

Blessed G, Black SE, Butler T, Kay DW. The diagnosis of dementia in the elderly. A comparison of CAMCOG (the cognitive section of CAMDEX), the AGECAT program, DSM-III, the Mini-Mental State Examination and some short rating scales. Br J Psychiaty 1991; 159: 193-198.

Block W, Karitzky J, Traber F, Pohl C, Keller E, Mundegar RR, Lamerichs R, Rink H, Ries F, Schild HH, Jerusalem F. Proton magnetic resonance spectroscopy of the primary motor cortex in patients with motor neuron disease: subgroup analysis and follow-up measurements. Arch Neurol 1998; 55: 931-936.

Block W, Traber F, Flacke S, Jessen F, Pohl C, Schild H. In vivo proton MR-spectroscopy of the human brain: assessment of N-acetylaspartate (NAA) reduction as a marker for neurodegeneration. Amino Acids 2002; 23: 317-323.

Blocq P & Marinesco G. Sur les lesions et la pathogenie de l'epilepsie dite essentiele. Sem med (Paris) 1892; 12: 445.

Bookheimer SY, Stroywas MH, Cohen MS, Saunders AM, Pericak-Vance MA, Mazziotta JC, Small GW. Patterns of brain activation in people at risk of Alzheimer's disease. N Engl J Med 2000; 343: 450-456.

Boss MA. Diagnostic approaches to Alzheimer's disease. Biocjem Biophys Acta 2000; 1502: 188-200.

Boyle PA, Wilson RS, Aggarwal NT, Tang Y, Bennett A. Mild cognitive impairment: risk of Alzheimer disease and rate of cognitive decline. Neurology 2006; 67: 441-445.

Braak H, Braak E. Alzheimer's disease: striatal amyloid deposits and neurofibrillary changes. J Neuropathol Exp Neurol 1990; 49: 215-224.

Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 1991; 82: 239-259.

Braak H, Braak E. Staging of Alzheimer's disease-related neurofibrillary changes. Neurobiol Aging 1995; 16: 271-278.

Braak H, Braak E. Evolution of neuronal changes in the course of Alzheimer's disease. J Neural Transm Suppl 1998; 53: 127-140.

Braak E, Griffing K, Arai K, Bohl J, Bratzke H, Braak H. Neuropathology of Alzheimer's disease: what is new since A Alzheimer? Eur Arch Psychiatry Clin Neurosci 1999; 249 (suppl 3): 13-22.

Brookmeyer R, Gray S, Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. Am J Public Health 1998; 88: 1337-1342.

Brooks WM, Stidley CA, Petropoulos H, Jung RE, Weers DC, Friedman SD, Barlow MA, Sibbitt WL Jr, Yeo RA. Metabolic and cognitive response to human traumatic brain injury: a quantitative proton magnetic resonance study. J Neurotrauma 2000; 17: 629-640.

Brun A, Englund E. Regional pattern of degeneration in Alzheimer's disease: neuronal loss and histopathological grading. Histopathology 1981; 5: 549-564.

Burger PC, Vogel FS. The development of the pathogenic changes of Alzheimer's disease and senile dementia in patients with Down's syndrome. Am J Pathol 1973; 73: 457-476.

Burns A, Philpot M, Costa D, Jell P, Levy R. The investigation of Alzheimer's disease with single photon emission tomography. J Neurol Neurosurg Psychiatry 1989; 52: 248-253.

Burt DB, Aylward EH. Test battery for the diagnosis of dementia in individuals with intellectual disability. Working Group for the Establishment of Criteria for the Diagnosis of Dementia in Individuals with Intellectual Disability. J Intellect Disabil Res 2000, 44, 175–180.

Burton EJ, Barber R, Mukaetova-Ladinska EB, Robson J, Perry RH, Jaros E, Kalaria RN, O'Brien JT. Medial temporal lobe atrophy on MRI differentiates Alzheimer's disease from dementia with Lewy bodies and vascular cognitive impairment: a prospective study with pathological verification of diagnosis. Brain 2009; 132: 195-203.

Callen DJA, Black SE, Gao F, Caldwell CB, Szalai JP. Beyond the hippocampus: MRI volumetry confirms widespread limbic atrophy in AD. Neurology 2001; 57: 1667-1674.

Capizzano AA, Schuff N, Amend DL, Tanabe JL, Norman D, Maudsley AA, Jagust W, Chui HC, Fein G, Segal MR, Weiner MW. Subcortical ischemic vascular

dementia: assessment with qualitative MR imaging and $^{1}H$ MR spectroscopy. Am J Neuroradiol 2000; 21: 621-630.

Carr J. Intellectual and daily living skills of 30-year-olds with Down's syndrome: Continuation of a longitudinal study. J Appl Res Intellect Disabil 2000; 13: 1-16.

Cendes F, Caramanos Z, Andermann F, Dubeau F, Arnold DL. Proton magnetic resonance spectroscopic imaging and magnetic resonance volumetry in the lateralization of temporal lobe epilepsy: a series of 100 patients. Ann Neurol 1997; 42: 737-746.

Cardenas VA, Du AT, Hardin D, Ezekiel F, Weber P, Jagust WJ, Chui HC, Schuff N, Weiner MW. Comparison of methods for measuring longitudinal brain change in cognitive impairment and dementia. Neurobiol Aging 2003; 24: 537-544.

Cardenas VA, Chao LL, Studholme C, Yaffe K, Miller BL, Madison C, Buckley ST, Mungas D, Schuff N, Weiner MW. Brain atrophy associated with baseline and longitudinal measures of cognition. Neurobiol Aging 2011; 32: 572-580.

Caramelli P, Robitaille Y, Laroche-Cholette A, Nitrini R, Gauvreau D, Joanette Y, Lecours AR. Structural correlates of cognitive deficits in a selected group of patients with Alzheimer's disease. Neuropsychiatry Neuropsychol Behav Neurol 1998; 11: 184-190.

Celsis P. Age-related cognitive decline, mild cognitive impairment or preclinical Alzheimer's disease? Ann Med 2000; 32: 6-14.

Chan D, Fox NC, Jenkins R, Scahill RI, Crum WR, Rossor MN. Rates of global and regional cerebral atrophy in AD and frontotemporal dementia. Neurology 2001; 57: 1756-1763.

Chantal S, Labelle M, Bouchard R. Correlation of regional proton magnetic resonance spectroscopy metabolic changes in mild Alzheimer's disease. Arch Neurol 2002; 59: 955-962.

Chantal S, Braun CM, Bouchard RW, Labelle M, Boulanger Y, Similar 1H magnetic resonance spectroscopic metabolic pattern in the medial temporal lobes of patients with mild cognitive impairment and Alzheimer's disease. Brain Res 2004; 1003: 26-35.

Chen P, Ratcliff G, Belle SH, Cauley JA, DeKosky ST, Ganguli M. Cognitive tests that best discriminate between presymptomatic AD and those who remain nondementia. Neurology 2000; 55: 1847-1853.

Christiansen P, Henriksen O, Stubgaard M, Gideon P, Larsson HB. In vivo quantification of brain metabolites by $^{1}$H-MRS using water as an internal standard. Magn Reson Imaging 1993; 11: 107-118.

Coffey CE, Wilkinson WE, Parashos IA, Soady SA, Sullivan RJ, Patterson LJ, Figiel GC, Webb MC, Spritzer CE, Djang WT. Quantitative cerebral anatomy of the aging human brain: a cross-sectional study using magnetic resonance imaging. Neurology 1992; 42: 527-536.

Conel JL. The brain structure of the newborn infant and consideration of the senile brain. In: The inter-relationship of mind and body. Vol. XIX. Cambridge, MA: Harvard University Press, Association for Research in Nervous and Mental Health 1939; pp 247-255.

Convit A, de Leon MJ, Golomb J, George AE, Tarshish CY, Bobinski M, Tsui W, De Santi S, Wegiel J, Wisniewski H. Hippocampal atrophy in early Alzheimer's disease, anatomic specificity and validation. Psychiatr Q 1993; 64: 371-387.

Convit A, de Leon MJ, Tarshish C, De Santi S, Tsui W, Rusinek H, George A. Specific hippocampal volume reductions in individuals at risk for Alzheimer's disease. Neurobiol Aging 1997; 18: 131-138.

Convit A, de Asis J, de Leon MJ, Tarshish CY, De Santi S, Rusinek H. Atrophy of the medial occipitotemporal, inferior and middle temporal gyri in non-demented elderly predict decline to Alzheimer's disease. Neurobiol Aging 2000; 21: 19-26.

Coppus A, Evenhuis H, Verberne GJ, Visser F, van Gool P, Eikelenboom P, van Duijin C. Dementia and mortality in persons with Down's syndrome. J Intellectual Disability Research 2006; 50: 768-777.

Cuenod CA, Denys A, Michot JL, Jehenson P, Forette F, Kaplan D, Syrota A, Boller F. Amygdala atrophy in Alzheimer's disease. An in vivo magnetic resonance imaging study. Arch Neurol 1993; 50: 941-945.

Cupples LA, Farrer LA, Sadovnick AD, Relkin N, Whitehouse P, Green. Genet Med 2004; 6: 192-196.

Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis I: segmentation and surface reconstruction. Neuroimaging 1999; 9: 179-194.

Davies P. Studies on the neurochemistry of central cholinergic systems in Alzheimer's disease: senile dementia and related disorders. New York: Raven Press 1978; pp 453-459.

Deb S & Bragnanza J. Comparison of rating scales for the diagnosis of dementia in adults with Down's syndrome. J Intellect Disabil Res 1999; 43: 400-407.

De la Monte MS. Quantitation of cerebral atrophy in preclinical and end-stage Alzheimer's disease. Ann Neurol 1989; 25: 450-459.

De la Monte SM, Hedley-Whyte ET. Small cerebral hemispheres in adults with Down's syndrome: contribution of developmental arrest and lesions of Alzheimer's disease. J Neuropathol Exp Neurol 1990; 49: 509-520.

De Leon M, George A, Convit A, Tarshish CY, McRae T, De Santi S, Smith G, Ferris SH, Noz M. The radiologic prediction of Alzheimer disease: the atrophic hippocampal formation. AJNR Am J Neuroradiol 1993; 14: 897-906.

De Leon MJ, Convit A, De Santi S, Bobinski M, George AE, Wisniewski HM, Rusinek H, Carroll R, Saint Louis LA. Contribution of structural neuroimaging to the early diagnosis of Alzheimer's disease. Int Psychogeriatr, 1997; 9 (suppl 1): 183-190.

De Santi S, de Leon MJ, Rusinek H, Convit A, Tarshish CY, Roche A, Tsui WH, Kandil E, Boppana M, Daisley K, Wang GJ, Schlyer D, Fowler. Hippocampal formation glucose metabolism and volume losses in MCI and AD. Neurobiol Aging 2001; 22: 529-539.

De Stefano N, Narayanan S, Francis GS. Evidence of axonal damage in the early stages of multiple sclerosis and its relevance to disability. Arch Neurol 2001; 58: 65-70.

De Toledo-Morrell L, Goncharova I, Dickerson B, Wilson RS, Bennett DA. From healthy aging to early Alzheimer's disease: in vivo detection of entorhinal cortex atrophy. Ann NY Acad Sci 2000; 911: 240-253.

Demougeot C, Marie C, Giroud M, Beley A. N-acetylaspartate: a literature review of animal research on brain ischaemia. J Neurochemistry 2004; 90: 776-783.

Department of Health. Living with dementia. A National Dementia Strategy. London, UK. Department of Health, 2009.

Devinsky O, Sato S, Conwit RA, Schapiro MB. Relation of EEG alpha background to cognitive function, brain atrophy, and cerebral metabolism in Down's syndrome: age-specific changes. Arch Neurol 1990; 47: 58-62.

Dickerson BC, Goncharova I, Sullivan MP, Forchetti C, Wilson RS, Bennett DA, Beckett LA, deToledo-Morrell L. MRI derived entorhinal and hippocampal atrophy in incipient and very mild Alzheimer's disease. Neurobiol Aging 2001; 22: 747-754.

Dickerson BC, Bakkour A, Salat DH, Feczko E, Pacheco J, Greve DN, Grodstein F, Wright CI, Blacker D, Rosas HD, Sperling RA, Atri A, Growdon JH, Hyman BT, Morris JC, Fischl B, Buckerner RL. The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild AD dementia and is detectable in asymptomatic amyloid positive individuals. Cereb Cortex 2009; 19: 497-510.

Donix M, Burggren AC, Suthana NA, Siddarth P, Ekstrom AD, Krupa AK, Jones M, Martin-Harris L, Ercoli LM, Miller KJ, Small GW, Bookheimer SY. Family history of Alzheimer's disease and hippocampal structure in healthy people. Am J Psychiatry 2010; 167: 1399-1406.

Doraiswamy PM, Charles HC, Krishnan KR. Prediction of cognitive decline in early Alzheimer's disease. Lancet 1998; 352: 1678.

Double KL, Halliday GM, Kril JJ, Harasty JA, Cullen K, Brooks WS, Creasey H, Broe GA. Topography of brain atrophy during normal ageing and AD. Neurobiology of Aging 1996; 17: 513-521.

Du AT, Schuff N, Amend D, Laakso M, Hsu Y, Jagust W, Yakke K, Kramer J, Reed B, Norman D, Chui H, Weiner M. Magnetic resonance imaging of the entorhinal cortex and hippocampus in mild cognitive impairment and Alzheimer's disease. J Neurol Neurosurg Psychiatry 2001; 71: 441-447.

Du AT, Schuff N, Zhu XP, Jagust WJ, Miller BL, Reed BR, Kramer JH Mungas D, Yaffe K, Chui HC, Weiner MW. Atrophy rates of entorhinal cortex in AD and normal aging. Neurology 2003; 60: 481-486.

Du AT, Schuff N, Kramer JH, Ganzer S, Zhu XP, Jagust WJ, Miller BL, Reed BR, Mungas D, Yaffe K, Chui HC, Weiner MW. Higher atrophy rate of entorhinal cortex than hippocampus in AD. Neurology 2004; 62: 422-427.

Du AT, Schuff N, Kramer JH, Rosen HJ, Gorno-Tempini ML, Rankin K, Miller BL, Weiner MW. Different regional patterns of cortical thinning in Alzheimer's disease and frontotemporal dementia. Brain 2007; 130: 1159-1166.

Eberling JL, Jagust WJ, Reed BR, Baker MG. Reduced temporal lobe blood flow in Alzheimer's disease. Neurobiol Aging 1992; 13: 483-491.

Elias MF, Beiser A, Wolf PA, Au R, White RF, D'Agostino RB. The preclinical phase of Alzheimer disease: a 22 year prospective study of the Framingham cohort. Arch Neurol 2000; 57: 808-813.

Emanuel I. An assessment of maternal intergenerational factors in pregnancy outcome. Am J Epidemiol 1997; 146: 820-825.

Emilsson L, Saetre P, Jazin E. Alzheimer's disease: mRNA expression profiles of multiple patients show alterations of gene involved with calcium signalling. Neurobiol dis 2006; 21: 618-625.

Erkinjuntti T, Lee DH, Gao F, Steenhuis R, Eliasziw M, Fry R, Merskey H, Hachinski VC. Temporal lobe atrophy on magnetic resonance imaging in the diagnosis of early Alzheimer's disease. Arch Neurol 1993; 50: 305-310.

Ernst T, Chang L, Melchor R, Mehringer CM. Frontotemporal dementia and early Alzheimer disease: differentiation with frontal lobe H-1 MR spectroscopy. Radiology 1997; 203: 829-836.

Evans DA, Funkenstein HH, Albert MS, Scherr PA, Cook NR, Chown MJ, Hebert LE, Hennekens CH, Taylor JO. Prevalence of Alzheimer's disease in a community population of older persons. Higher than previously reported. JAMA 1989; 262: 2551-2556.

Fagan AM, Holtzman DM, Munson G, Mathur T, Schneider D, Chang LK, Getz GS, Reardon CA, Lukens J, Shah JA, LaDu MJ. Unique lipoproteins secreted by primary astrocytes from wild type, apoE (-/-) and human apoE transgenic mice. J Biol Chem 2000; 274: 30001-30007.

Farrer LA, Cupples LA, Connor L, Wolf PA, Growdon JH. Association of decreased paternal age and late-onset Alzheimer's disease. An example of genetic imprinting? Arch Neurol 1991; 48: 599-604.

Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N, Van Duijn CM. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA 1997; 278: 1349-1356.

Fernandez A, Garcia-Segura JM, Ortiz T, Montoya J, Maestu F, Gil-Gregorio P, Campo P, Viano J. Proton magnetic resonance spectroscopy and magnetoencephalographic estimation of delta dipole density: a combination of techniques that may contribute to the diagnosis of Alzheimer's disease. Dement Geriatr Cogn Disord 2005; 20: 169-177.

Ferri CP, Prince M, Brayne C, Bodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Paulo RM, Rimmer E, Scazufca M. Global prevalence of dementia: a Delphi consensus study. Lancet 2005; 366: 2112-2117.

Filler AG. The history, development and impact of computer imaging in neurological diagnosis and neurosurgery: CT, MRI, DTI. Nature Preceedings 2009. DOI: 10.1038/npre.2009.3267.4.

Fischl BR, Sereno MI, Dale AM, Cortical surface-based analysis II : inflation, flattening and surface-based coordinate system, Neuroimage 1999; 9: 195-207.

Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci USA 2000; 97: 11050-11055.

Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B, Dale AM. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 2002; 33: 341-355.

Fischl B, van der Kouwe A, Destrieux C, Halgren E, Segonne F, Salat DH, Bus E, Seidman LJ, Goldstein J, Kennedy D, Cavniess V, Makris N, Rosen B, Dale AM, Automatically parcellating the human cerebral cortex. Cereb Cortex 2004; 14: 11-22.

Fitzpatrick AL, Kuller LH, Lopez OL, KAwas CH, Jagust W. Survival following dementia onset: Alzheimer's disease and vascular dementia. J Neurol Sci 2005; 229: 43-49.

Flicker C, Ferris SH, Reisberg B. Mild cognitive impairment in the elderly: predictors of dementia. Neurology 1991; 41: 1006-1009.

Folin M, Baiguera S, Conconi MT, Pati T, Grandi C, Parnigotto PP, Nussdorfer GG. The impact of risk factors of Alzheimer's disease in the Down syndrome. Int J Mol Med 2003; 11: 267-270.

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189-198.

Fox NC, Freeborough PA, Rossor MN. Visualisation and quantification of rates of atrophy in Alzheimer's disease. Lancet 1996; 348: 94-97.

Fox PT. The growth of human brain mapping. Hum Brain Mapp 1997; 5: 1-2.

Fox NC, Scahill RI, Crum, WR, Rossor MN. Correlation between rates of brain atrophy and cognitive decline in AD. Neurology 1999a; 52: 1687-1689.

Fox NC, Rossor MN. Diagnosis of early Alzheimer's disease. Rev Neurol 1999b; 155 (suppl 4): S33-S37.

Fox NC, Cousens S, Scahill R, Harvey RJ, Rossor MN. Using serial registered brain magnetic resonance imaging to measure disease progression in Alzheimer's disease: power calculations and estimates of sample size to detect treatment effects. Arch Neurol 2000; 57: 339-344.

Fox NC, Crum WR, Scahill RI, Stevens JM, Janssen JC, Rossor MN. Imaging of onset and progression of Alzheimer's disease with voxel-compression mapping of serial magnetic resonance images. Lancet 2001; 358: 201-205.

Fradinger EA & Bitan G. En route to early diagnosis of Alzheimer's disease – are we there yet. Trends in Biotechnology 2005; 23: 531-533.

Frisoni GB. Structural imaging in the clinical diagnosis of Alzheimer's disease: problems and tools. J Neurol Neurosury Psychiatry 2001; 70: 711-718.

Frisoni GB Scheltens P, Galluzzi S, Nobili FM, Fox NC, Robert PH. Neuroimaging tools to rate regional atrophy, subcortical cerebrovascular disease, and regional cerebral blood flow and metabolism: consensus paper of the EADC. J Neurol Neurosurg Psychiatry 2003; 74: 1371-381.

Fritsch T, McClendon MJ, Smyth KA, Ogrocki PK. Effects of educational attainment and occupational statuson cognitive and functional decline in persons with Alzheimer-type dementia. Int Psychogeriatr 2002; 14: 347-363.

Galasko DR, Gould RL, Abramson IS, Salmon DP. Measuring cognitive change in a cohort of patients with Alzheimer's disease. Stat Med 2000; 19: 1421-1432.

Galdzicki Z, Siarey R, Pearce R, Stoll J, Rapaport SI. On the cause of mental retardation in Down syndrome: extrapolation from full and segmental trisomy 16 mouse models. Brain Res Brain Res Rev 2001; 35: 115-145.

Ganguli M, Dodge HH, Shen C, Pandav RS, DeKosky ST. Alzheimer disease and mortality: a 15 year epidemiological study. Arch Neurol, 2005; 62: 779-784.

Geroldi C, Laakso MP, DeCarli C, Beltramello A, Bianchetti A, Soininen H, Trabucchi M, Frisoni G. Apolipoprotein E genotype and hippocampal asymmetry in Alzheimer's disease: a volumetric MRI study. J Neurol Neurosurg Psychiatry 2000; 68: 93-96.

Geslani D, Tierney M, Herrmann N, Szalai J. Mild cognitive impairment: an operational definition and its conversion rate to Alzheimer's disease. Dement Geriatr Cogn Discord 2005; 19: 383-389.

Giesel FL, Hahn HK, Thomann PA, Widjaja E, Wignall E, von Tengg-Kobligk H, Pantel J, Griffiths PD, Peitgen HO, Schroder J, Essig M. Temporal horn index and volume of medial temporal lobe atrophy using a new semiautomated method for rapid and precise assessment. Am J Neuroradiol 2006; 27: 1454-1458.

Golomb J, Kluger A, de Leon M, Ferris SH, Convit A, Mittleman M, Cohen J, Rusinek H, De Santi S, George AE. Hippocampal formation size in normal human aging: a correlate of delayed secondary memory performance. Learn Mem 1994; 1: 45-54.

Golomb J, Kluger A, de Leon M, Ferris SH, Mittelman M, Cohen J, George AE. Hippocampal formation size predicts declining memory performance in normal aging. Neurology 1996; 47: 810-813.

Gosche KM, Mortimer JA, Smith CD, Markesbery WR, Snowdon DA. Hippocampal volume as an index of Alzheimer neuropathology: findings from the Nun study. Neurology 2002; 58: 1476-1482.

Gundersen, H. J. & Jensen, EB. The efficiency of systematic sampling in stereology and its prediction. J Microscopy 1987; 147: 229-263.

Green RC, Cupples LA, Go RCPG, Benke KS, Edeki T, Griffith PA, Wiliiams M, Hipps Y, Graff-Radford N, Bachman D, Farrer LA, for the MIRAGE Study Group. Risk of dementia among white and African American relatives of patients with Alzheimer's disease. JAMA 2002; 287: 329-336.

Grehan S, Tse E, Taylor JM. Two distal downstream enhancers direct expression of the human apolipoprotein E gene to astrocytes in the brain. J Neurosci 2001; 21: 812-822.

Groen W, Teluji M, Buitelaar J, Tendolkar I. Amygdala and hippocampus enlargement during adolescence in autism. J Am Acad Child Adol Psychiatry 2010; 49: 552-560.

Grundman M, Petersen RC, Ferris SH, Thomas RG, Aisen PS, Bennett DA, Foster NL, Jack CR Jr, Galasko DR, Doody R, Kaye J, Sano M, Mohs R, Gauthier S, Kim HT, Jin, Schultz AN, Schafer K, Mulnard R, van Dyck CH, Mintzer J, Zamrini EY, Cahn-Weiner D, Thal LJ. Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. Arch Neurol 2004; 61: 59-66.

Grut M, Fratiglioni L, Viitanen M, Winblad B. Accuracy of the Mini-Mental Status Examination as a screening test for dementia in a Swedish elderly population. Acta Neurol Scand 1993; 87: 312–317.

Haier RJ, Alkire MT, White NS, Uncapher RM, Head E, Lott IT, Cotman CW. Temporal cortex hypermetabolism in Down syndrome prior to the onset of dementia. Neurology 2003; 61: 1673-1679.

Hampel H, Teipel SJ, Alexander GE, Horwitz B, Teichberg D, Schapiro M, Rapoport SI. Corpus callosum atrophy is a possible indicator for region and cell type specific neuronal degeneration in Alzheimer's disease: an MRI analysis. Arch Neurol 1998; 55: 193-198.

Hampel H, Teipel SJ, Bayer W, Alexander GE, Schwarz R, Schapiro MB, Rapoport SI, Moller HJ. Age transformation of combined hippocampus and amygdala volume improves diagnostic accuracy in Alzheimer's disease. J Neurol Sci 2002; 194: 15-19.

Hanninen T, Hallikainen M, Tuomainen S, Vanhanen M, Soininen H. Prevalence of mild cognitive impairment: a population-based study in elderly subjects. Acta Neurol Scand 2002; 106: 148-154.

Hansen LA, DeTeresa R, Davies P, Terry RD. Neocortical morphometry, lesion counts, and choline acetyltransferase levels in the age spectrum of Alzheimer's disease. Neurology 1988; 38: 48-54.

Harvan JR, Cotter V. An evaluation of dementia screening in the primary care setting. J Am Acad Nurse Pract 2006; 18: 351-360.

Hessl D, Rivera S, Koldewyn K, Cordeiro L, Adams J, Tassone F, Hagerman PJ, Hagerman RJ. Amygdala dysfunction in men with the fragile X premutation. Brain 2007; 130: 404-416.

Heun R, Schlegel S, Graf-Morgenstern M, Tintera J, Gawehn J, Stoeter P. Proton magnetic resonance spectroscopy in dementia of Alzheimer type. Int J Geriatr Psychiatry 1997; 12: 349-358.

Ho AJ, Hua X, Lee S, Leow AD, Yanovsky I, Gutman B, Dinov ID, Lepore N, Stein JL, Toga AW, Jack CR Jr, Harvey DJ, Kornak J, Schuff N, Alexander GE, Weiner MW, Thompson PM. Comparing 3 T and 1.5 T MRI for tracking Alzheimer's disease progression with tensor-based morphometry. Hum Brain Mapp 2010; 31: 499-514.

Hof PR, Bouras C, Perl DP, Sparks L, Mehta N, Morrison JH. Age-related distribution of neuropathologic changes in the cerebral cortex of patients with Down's syndrome: quantative regional analysis and comparison with Alzheimer's disease. Arch Neurol 1995; 52: 379-391.

Hon J, Huppert FA, Holland AJ, Watson P. Neuropsychological assessment of older adults with Down's syndrome: an epidemiological study using the Cambridge Cognitive Examination (CAMCOG). Br J Clin Psychol 1999; 38: 155-165.

Hua X, Lee S, Yanovsky I, Leow AD, Chou YY, Ho AJ, Gutman B, Toga AW, Jack CR Jr, Bernstein MA, Reiman EM, Harvey DR, Kornak J, Schuff N, Alexander GE, Weiner MW, Thompson PM, Alzheimer's Disease Neuroimaging Initiative. Optimizing power to track brain degeneration in Alzheimer's disease and mild cognitive impairment with tensor-based morphometry: an ADNI study of 515 subjects. NeuroImage 2009; 48: 668-681.

Huang W, Alexander GE, Daly EM, Shetty HU, Krasuski JS, Rapoport SI, Schapiro MB. High brain myo-inositol levels in the predementia phase of Alzheimer's disease in adults with Down's syndrome: a 1H-MRS study. Am J Psychiatry 1999; 156: 1879-1886.

Huang W, Alexander GE, Chang L, Shetty HU, Krasuski JS, Rapoport SI, Schapiro MB. Brain metabolite concentration and dementia severity in Alzheimer's disease: a $^{1}$H MRS study. Neurology 2001; 57: 626–632.

Hugg JW, Kuzniecky RI, Gilliam FG, Morawetz RB, Fraught RE, Hetherington HP. Normalization of contralateral metabolic function following temporal lobectomy demonstrated by 1H magnetic resonance spectroscopic imaging. Ann Neurol 1996; 40: 236-239.

Huppert FA, Brayne C, Gill C, Paykel ES, Beardsall L. CAMCOG-A concise neuropsychological test to assist dementia diagnosis: socio-demographic determinants in an elderly population sample. J Clin Psychology 1995; 34: 529-541.

Hyman BT, Van Hoesen GW, Damasio AR, Barnes CL. Alzheimer's disease: cell-specific pathology isolates the hippocampal formation. Science 1984; 225: 1768-1170.

Hyman BT, Van Hoessen GW, Kromer LJ, Damasio AR. Perforant pathway changes in the memory impairment of Alzheimer's disease. Ann Neurol 1986; 20: 472-481.

Hyman BT, West HL, Rebeck GW, Lai F, Mann DMA. Neuropathological changes in Down's syndrome hippocampal formation: effect of age and apolipoprotein E genotype. Arch Neurol 1995; 52: 373-378.

Ikeda M, Arai Y. Londitudinal changes in brain CT scans and development of dementia in Down's syndrome. Eur Neurol 2002; 47: 205-208.

Jack CR Jr, Petersen RC, O'Brien PC, Tangalos EG. MR-based hippocampal volumetry in the diagnosis of Alzheimer's disease. Neurology 1992; 42: 183-188.

Jack CR Jr, Petersen RC, Xu YC, Waring SC, O'Brien PC, Tangalos EG, Smith GE, Ivanik RJ, Kokmen E. Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease. Neurology 1997; 49: 786-794.

Jack CR Jr., Petersen RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ, Tangalos EG, Kokmen E. Rate of medial temporal lobe atrophy in typical aging and Alzheimer's disease. Neurology 1998; 51: 993–999.

Jack CR Jr, Petersen RC, Xu TC, O'Brien PC, Smith GE, Ivnik RJ, Boeve BF, Waring SC, Tangalos EG, Kokmen E. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. Neurology 1999; 52: 1397-1403.

Jack CR Jr., Petersen RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ, Boeve BF, Tangalose EG, Kokmen E. Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. Neurology 2000; 55: 484–489.

Jack CR, Slomkowski M, Gracon S, Hoover TM, Felmlee JP, Stewart J, Xu Y, Shiung M, O'Brien PC, Cha R, Knopman D, Petersen RC. MRI as a biomarker of disease progression in a therapeutic trial of milameline for AD. Neurology 2003; 60: 253-260.

Jack CR Jr, Shiung MM, Gunter JL, O'Brien PC, Weigand SD, Knopman DS, Boeve BF, Ivnik RJ, Smith GE, Cha RH, Tangalos EG, Petersen RC. Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD. Neurology 2004; 62: 591–600.

Jack CR Jr, Shiung MM, Weigand SD, O'Brien PC, Gunter JL, Boeve BF, Knopman DS, Smith GE, Ivnik RJ, Tangalos EG, Petersen RC. Brain atrophy rates predict subsequent clinical conversion in normal elderly and amnestic MCI. Neurology 2005; 65: 1227-1231.

Janowsky JS, Kaye JA, Carper RA. Atrophy of the corpus callosum in Alzheimer's disease versus healthy aging. J Am Geriatr Soc 1996; 44: 789-803.

Jernigan TL, Archibald SL, Berhow MT, Sowell ER, Foster DS, Hesselink JR. Cerebral structure on MRI, part 1: localization of age-related changes. Biol Psychiatry 1991; 29: 55-67.

Jernigan TL, Bellugi U, Sowell E, Doherty S, Hesselink JR. Cerebral morphologic distinctions between Williams and Down syndromes. Arch Neurol 1993; 50: 186-191.

Jessen F, Block W, Traber F, Keller E, Flacke S, Papassotiropoulos A, Lamerichs R, Heun R, Schild HH. Proton MR spectroscopy detects a relative decrease of N-acetylaspartate in the medial temporal lobe of patients with AD. Neurology 2000; 55: 684-688.

Jethwa H, Cassidy G. Difficulties of dealing with dementia in individuals with intellectual disabilities: the healthcare perspective. Advances in Mental Health and Intellectual Disabilities 2010; 4: 48-52

Jobst KA, Smith AD, Barker CS. Association of atrophy of the medial temporal lobe with reduced blood flow in the posterior parietotemporal cortex in patients with a clinical and pathological diagnosis of Alzheimer's disease. J Neurol Neurosurg Psychiatry 1992; 55: 190-194.

Johnson SC, Schmitz TW, Trivedi MA, Ries ML, Torgerson BM, Carlsson CM, Asthana S, Hermann BP, Sager MA. The influence of Alzheimer disease family history and apolipoprotein E epsilon 4 on mesial temporal lobe activation. J Neurosci 2006; 26: 6069-6076.

Jonker C, Geerlings MI, Schmand B. Are memory complaints predictive for dementia? A review of clinical and population-based studies. Int J Geriatr Psychiatry 2000; 15: 983-991.

Joseph KS, Kramer MS. Review of the evidence on fetal and early childhood antecedents of adult chronic disease. Epidemiol Rev 1996; 18: 158-174.

Josephs KA, Whitwell JL, Ahmed Z, Shiung MM, Weigand SD, Knopman DS, Boeve BF, Parisi JE, Petersen RC, Dickson DW, Jack CR Jr. β-amyloid burden is not associated with rates of brain atrophy. Ann Neurol 2008; 63: 204-212.

Juottonen K, Lehtovirta M, Helisalmi S, Soininen H. Major decrease in the volume of the entorhinal cortex in patients with Alzheimer's disease carrying the apolipoprotein E ε4 allele. J Neurol Neurosurg Psychiatry 1998; 65: 322-327.

Juottonen K, Laakso MP, Partanen K, Soininen H. Comparative MR analysis of the entorhinal cortex and hippocampus in diagnosing Alzheimer disease. Am J Neuroradiology 1999; 20: 139-144.

Kalaria RN, Maestre GE, Arizaga R, Friedland RP, Galasko D, Hall K. Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. Lancet Neurol 2008; 7: 812-826.

Kantarci K, Jack CR Jr, Xu YC, Campeau NG, O'Brien PC, Smith GE, Ivnik RJ, Boeve BF, Kokmen E, Tangalos EG, Petersen RC. Regional metabolic patterns in

mild cognitive impairment and Alzheimer's disease: a 1H MRS study. Neurol 2000; 55: 210-217.

Kantarci K, Xu Y, Shiung MM, O'Brien PC, Cha RH, Smith GE, Ivnik RJ, BoeveBF, Edland DS, Kokman E, Tangalos EG, Petersen RC, Jack CR Jr. Comparative diagnostic utility of different MR modalities in mild cognitive impairment and Alzheimer's disease. Dement Geriatr Cogn Disord 2002; 14: 198-207.

Kantarci K, Petersen RC, Boeve BF, Knopman DS, Tang-Wai DF, O'Brien PC, Weigand SD, Edland SD, Smith GE, Ivnik RJ, Ferman TJ, Tangalos EG, Jack CR Jr. 1H MR spectroscopy in common dementias. Neurol 2004; 63: 1393-1398.

Kantarci K. $^{1}$H magnetic resonance spectroscopy in dementia. Br J Radiology 2007; 80: 146-152.

Kantarci K, Knopman DS, Dickson DW, Parisi JE, Whitwell JL, Weigand SD, Josephs KA, Boeve BF, Petersen RC, Jack CR Jr. Alzheimer disease: post-mortem neuropathologic correlates of antemortem 1H MR spectroscopy metabolite measurements. Radiology 2008; 248: 210-220.

Karas GB, Burton EJ, Rombouts SA, van Schijndel RA, O'Brien JT, Scheltens P, McKeith IG, Williams D, Ballard C, Barkhof F. A comprehensive study of gray matter loss in patients with Alzheimer's disease using optimized voxel-based morphometry. Neuroimage 2003; 18: 895-907.

Karp A, Paillard-Borg S, Wang HX, Silverstein M, Winblad B, Fratiglioni L. Mental, physical and social components in leisure activities equally contribute to decrease dementia risk. Dement Geriatr Cogn Disord 2006; 21: 65-73.

Katzman R. Alzheimer's disease. N Engl J Med 1986; 314: 964-937.

Katzman R, Terry R, DeTeresa R, Brown T, Davies P, Fuld P, Renbing X, Peck A. Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. Ann Neurol 1988; 23: 138-144.

Kaye JA, Swihart T, Howieson D, Dame A, Moore MM, Karnost T, Camicioli R, Ball M, Oken B, Sexton G. Volume loss of the hippocampus and temporal lobe in healthy elderly persons destined to develop dementia. Neurology 1997; 48: 1297-1304.

Kesslak JP, Nalcioglu O, Cotman CW. Quantification of magnetic resonance scans for hippocampal and parahippocampal atrophy in Alzheimer's disease. Neurology 1991; 41: 51-54.

Kesslak JP, Nagata SF, Lott I, Nalcioglu O. Magnetic resonance imaing with Down's syndrome. Neurology 1994; 44: 1039-1045.

Killiany RJ, Moss MB, Albert MS, Sandor T, Tieman J, Jolesz F. Temporal lobe regions on magnetic resonance imaging identify patients with early Alzheimer's disease. Arch Neurol 1993; 50: 949-954.

Killiany RJ, Gomez-Isla T, Moss M, Kikinis R, Sandor T, Jolesz F, Tanzi R, Jones K, Hyman BT, Albert MS. Use of structural magnetic resonance imaging to predict who will get Alzheimer's disease. Ann Neurol 2000; 47: 430-439.

Killiany RJ, Hyman BT, Gomez-Isla T, Moss MB, Kikinis R, Jolesz F, Tanzi R, Jones K, Albert MS. MRI measures of entorhinal cortex vs hippocampus in preclinical Alzheimer's disease. Neurology 2002; 58: 1188-1196.

Knopman DS, DeKosky ST, Cummings JL. Practice parameter: diagnosis of dementia (an evidence-based review). Neurology 1991; 56: 1143-1153.

Knopman DS, Dekosky ST, Cummings JL, Chui H, Corey-Bloom J. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001; 56: 1143-1153.

Koepsell TD, Kurland BF, Harel O, Johnson EA, Zhou XH, Kukull WA. Education, cognitive function, and severity of neuropathology in Alzheimer disease. Neurology 2008; 70: 1732-1739.

Krasuski JS, Alexander GE, Horwitz B, Daly EM, Murphy DG, Rapoport SI, Schapiro MB. Volumes of medial temporal lobe structures in patients with Alzheimer's disease and mild cognitive impairment (and in healthy controls). Biol Psychiatry 1998; 43: 60-68.

Krasuski JS, Alexander GE, Horwitz B, Rapoport SI, Schapiro MB. Relation of medial temporal lobe volumes to age and memory function in nondemented adults with Down's syndrome: implications for the prodromal phase of Alzheimer's disease. Am J Psychiatry 2002; 159: 74-81.

Krishnan KR, Charles HC, Doraiswamy PM, Mintzer J, Weisler R, Yu X, Perdomo C, Ieni JR, Rogers S. Randomized, placebo-controlled trial of the effects of donepezil on neuronal markers and hippocampal volumes in Alzheimer's disease. Am J Psychiatry 2003; 160: 2003-2011.

Kwo-On-Yuen PF, Newmark RD, Budinger TF, Kaye JA, Ball MJ, Jagust WJ. Brain N-acetyl-L-aspartic acid in Alzheimer's disease: a proton magnetic resonance spectroscopy study. Brain Res 1994; 667: 167-174.

Laakso MP, Soininen H, Partanen K, Helkala EL, Hartikainen P, Vainio P, Hallikainen M, Hanninen T, Riekkinen PJ Sr. Volumes of hippocampus, amygdala and frontal lobes in the MRI-based diagnosis of early Alzheimer's disease: correlation with memory functions. J Neural Transm 1995; 9: 73-86.

Laakso MP, Hallkirainen M, Hanninen T, Partanen K, Soininen H. Diagnosis of Alzheimer's disease: MRI of the hippocampus vs delayed recall. Neurophychologia 2000; 38: 579-584.

Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L, Kockunov PV, Nickerson D, Mikiten SA, Fox PT. Automated Talairach atlas labels for functional brain mapping. Hum Brain Mapp 2000; 10: 120-131.

Larrieu S, Letenneur L, Orgogozo JM., Fabrigoule C, Armieva H, Le Carret N, Barberger-Gateau P, Dartigues JF. Incidence and outcome of mild cognitive impairment in a population-based prospective cohort. Neurology 2002; 59: 1594-1599.

Lazeyras F, Charles HC, Tupler LA, Erickson R, Boyko OB, Krishnan KR. Metabolic brain mapping in Alzheimer's disease using proton magnetic resonance spectroscopy. Psychiatry Res 1998; 82: 95-106.

Lehericy S, Baulac M, Chiras J, Pierot L, Martin N, Pillon, B, Deweer B, Dubois B, Marsault. Amygdalohippocampal MR volume measurements in the early stages of Alzheimer disease. AJNR Am J Neuroradiol 1994; 15: 929-937.

Lehericy S, Marjanska M, Mesrob L, Sarazin M, Kinkingnehun S. Magnetic resonance imaging of Alzheimer's disease. Eur Radiol 2007; 17: 347-362.

Lehtovirta M, Kuikka J, Helisalmi S. Longitudinal SPECT study in Alzheimer's disease: relation to apolipoprotein E polymorphism. J Neurol Neurosurg Psychiatry 1998; 64: 742-746.

Le May M, Alvarez N. The relationship between enlargement of the temporal horns of the lateral ventricles and dementia in aging patients with Down syndrome. Neuroradiology 1990; 32: 104-107.

Lerch JP, Pruessner JC, Zijdenbos A, Hampel H, Teipel SJ, Evans AC. Focal decline of cortical thickness in Alzheimer's disease identified by computational neuroanatomy. Cereb Crotex 2005; 15: 995-1001.

Letovsky SI, Whitehead SH, Paik, CH, Miller GA, Gerbert J, Herskovits EH, Fulton TK, Bryan RN. A brain image database for structure/function analysis. AJNR AM J Neuroradiol 1998; 19: 1869-1877.

Lewis DA, Campbell MJ, Terry RD, Morrison JH. Laminar and regional distribution of neurofibrillary tangles and neuritic plaques in Alzheimer's disease: a quantitative study of visual and auditory cortices. J Neurosci 1987; 7: 1799-1808.

Lezak MD, Howieson DB, Loring DW. Neuropsychological Assessment. 4th ed. Oxford University Press; Oxford, 2004.

Linn RT, Wolf PA, Bachman DL, Knoefel JE, Cobb JL, Belanger AJ, Kaplan EF, D'Agostino RB. The 'preclinical phase' of probable Alzheimer's disease. Arch Neurol 1995; 52: 485-490.

Liu H-C, Liu R-S, Lin K-N, Wang SJ, Fuh JL, Yeh SH, Chiang BN. Single photon emission computed tomography using 99Tcm-HMPAO in Alzheimer's disease. Nucl Med Commun 1992; 13: 535-541.

Lobo A, Launer LJ, Fratiglioi L, Andersen K, Di Carlo A, Breteler MMB, Copeland JRM, Dartigues JF, Jagger C, Martinez-Lage J, Soininen H, Hofman A. Prevalence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurological diseases in the elderly research group. Neurology 2000; 54 (11 suppl 5): S4-9.

Loos C, Achten E, Santens P. Proton magnetic resonance spectroscopy in Alzheimer's disease. Acta Neurol Belg 2010; 110: 291-298.

Lott IT, Lai FL. Dementia in Down syndrome (abstract). Ann Neurol 1982; 12: 210.

Lott IT, Head E. Down syndrome and Alzheimer's disease: a link between development and aging. Ment Retard Dev Disabil Res Rev 2001; 7: 172-178.

Lyketsos CG, Steinberg M, Tschanz JT, Norton MC, Steffens DC, Breitner JC. Mental and behavioural disturbances in dementia: findings from the Cache County study on memory and aging. Am J Psychiatry 2000; 157: 708-714.

McBrien J A., Whitwham S, Olverman K, Masters S. Screening adults with Down's syndrome for early signs of Alzheimer's disease. TLDR 2005; 10: 23-32.

MacKay S, Meyerhoff DJ, Constans JM, Norman D, Fein G, Weiner MW. Regional gray and white matter metabolite differences in subjects with AD, with subcortical ischemic vascular dementia, and elderly controls with 1H magnetic resonance spectroscopic imaging. Arch Neurol 1996; 53: 167-174.

Mahley RW, Weisgraber KH, Huang Y. Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease. PNAS 2006; 103: 5644-5651.

Mann DMA, Marcyniuk B, Yates PO, Neary D, Snowden JS. The progression of the pathologic changes of Alzheimer's disease in the frontal and temporal neocortex examined both at biopsy and autopsy. Neuropathol Appl Neurobiol 1988; 14: 177-195.

Mann DMA, Esiri MM. The pattern of acquisition of plaques and tangles in the brains of patients under 50 years of age with Down's syndrome. J Neurol Sci 1989; 89: 169-179.

Mann DMA, Royston MC, Ravindra CR. Some morphological observations on the brains of patients with Down's syndrome: their relationship to age and dementia. J Neurol Sci 1990; 99: 153.

Marjanska M, Curran GL, Wengenack TM, Henry PG, Bliss RL, Poduslo JF, Jack CR Jr, Ugurbil K, Garwood M. Monitoring disease progression in transgenic mouse

models of Alzheimer's disease with proton magnetic resonance spectroscopy. Proc Natl Acad Sci USA 2005; 102: 11906-11910.

Martinez-Bisbal MC, Arana E, Marti-Bonmati L, Molla E, Celda B. Cognitive impairment: classification by 1H magnetic resonance spectroscopy. Eur J Neurol 2004; 11: 187-93.

Masliah E, Mallory M, Hansen L, DeTeresa R, Alford M, Terry R. Synaptic and neuritic alterations during the progression of Alzheimer's disease. Neurosci Lett 1994; 174: 67-72.

Masliah E. The natural evolution of the neurodegenerative alterations in Alzheimer's disease, Neurobiol Aging 1995; 16: 280-282.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDS Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984; 34: 939-944.

McLaurin J, Franklin T, Chakrabartty A, Fraser PE. Phosphatidylinositol and inositol involvement in Alzheimer amyloid-beta fibril growth and arrest. J Mol Biol 1998; 278: 183-194.

McQuillan S, Kalsy S, Oyebode J, Millichap D, Oliver C, Hall S. Adults with Down's syndrome and Alzheimer's disease. TLDR 2003; 8: 4-13.

Mega MS, Thompson PM, Toga AW, Cummings JL. Brain mapping in dementia, in Mazziotta J Frackowiak RSJ, Toga A (eds), Brain Mapping: The Disorders, Academic Press, San Diego 2000; pp 217-239.

Melzer D, Ely M, Brayne C. Cognitive impairment in elderly people: Population based estimate of the future in England, Scotland and Wales. BMJ 1997; 315: 462.

Meyerhoff DJ, MacKay S, Bachman L, Poole N, Dillon WP, Weiner MW, Fein G. Reduced brain *N*-acetyl-aspartate suggests neuronal loss in cognitively impaired human immuno-deficiency virus-seropositive individuals: in vivo $^{1}H$ magnetic resonance spectroscopic imaging. Neurology 1993; 43: 509-515.

Meyerhoff DJ, MacKay S, Constans JM, Norman D, Van Dyke C, Fein G, Weiner MW. Axonal injury and membrane alterations in Alzheimer's disease suggested by in vivo proton magnetic resonance spectroscopic imaging. Ann Neurol 1994; 36: 40-47.

Miller BL, Moats RA, Shonk T, Ernst T, Woolley S, Ross BD. Alzheimer disease: depiction of increased cerebral myo-inositol with proton MR spectroscopy. Radiology 1993; 187: 433-437.

Minati L, Edginton T, Bruzzone MG, Giaccone G. Reviews: current concepts in Alzheimer's disease: a multidisciplinary review. Am J Alzheimers Dis Other Demen 2009; 24: 95-121.

Moats RA, Ernst T, Shonk TK, Ross BD. Abnormal cerebral metabolite concentrations in patients with probable Alzheimer disease. Magn Reson Med 1994; 32: 110-115.

Moceri VM, Kukull WA, Emanuel I, van Belle G, Larson EB. Early-life risk factors and the development of Alzheimer's disease. Neurology 2000; 54: 415-421.

Modrego PJ, Fayed N, Pina MA. Conversion from mild cognitive impairment to probable Alzheimer's disease predicted by brain magnetic resonance spectroscopy. Am J Psychiatry 2005; 162: 667-675.

Modrego PJ, Pina MA, Fayed N, Diaz M. Changes in metabolite ratios after treatment with rivastigmine in Alzheimer's disease: a nonrandomised controlled trial with magnetic resonance spectroscopy. CNS Drugs 2006; 20: 867-877.

Mohanakrishnan P, Fowler AH, Vonsattel JP, Jolles PR, Husain MM, Liem P, Meyers L, Komoroski RA. Regional metabolic alterations in Alzheimer's disease: an in vitro 1H NMR study of the hippocampus and cerebellum. J Gerontol Series A Biol Sci Med Sci 1997; 52: 111-117.

Mori E, Yoneda Y, Yamashita H, Hirono N, Ikeda M, Yamadori A. Medial temporal structures relate to memory impairment in Alzheimer's disease: an MRI volumetric study. J Neurol Neurosurg Psychiatry 1997; 63: 214-221.

Morra JH, Tu Z, Apostolova LG, Green AE, Avedissian C, Madsen SK, Hua X, Toga AW, Jack CR Jr, Schuff N, Weiner MW, Thompson PM, Alzheimer's Disease Neuroimaging Initiative. Automated 3D mapping of hippocampal atrophy and its clinical correlates in 400 subjects with Alzheimer's disease, mild cognitive impairment, and elderly controls. Hum Brain Mapp 2009; 30: 2766-2788.

Morris JC, Edland S, Clark C, Galasko D, Koss E, Mohs R, van Belle G, Fillenbaum G, Heyman A. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part IV. Rates of cognitive change in the longitudinal assessment of probable Alzheimer's disease. Neurology 1993; 43: 2457-2465.

Morris JC, Storandt M, Miller JP, McKeel DW, Price JL, Rubin EH, Berg L. Mild cognitive impairment represents early-stage Alzheimer's disease. Arch Neurol 2001; 58: 397-405.

Mosconi L, Brys M, Switalski R, Mistur R, Glodzik L, Pirraglia E, Tsui W, De Santi S, de Leon MJ. Maternal history of Alzheimer's disease predisposes to reduced brain glucose metabolism. Proc Natl Acad Sci USA 2007; 104: 19067-19072.

Mosconi L, Mistur R, Switalski R, Brys M, Glodzik L, Rich K, Pirraglia E, Tsui W, De Santi S, de Leon MJ. Declining brain glucose metabolism in normal individuals with a maternal history of Alzheimer's disease. Neurology 2009; 72: 513-520.

Mouton PR, Martin LJ, Calhoun ME, Dal Forno G, Price DL. Cognitive decline strongly correlates with cortical atrophy in Alzheimer's dementia. Neurobiol Aging 1998; 19: 371-377.

Mungas D, Marshall SC, Weldon M, Haan M, Reed BR. Age and education correction of Mini-Mental State Examination for English and Spanish-speaking elderly. Neurology 1996; 46: 700-706.

Murata T, Koshino Y, Omori Y, Murata I, Nishio M, Horie T, Umezawa Y, Isaki K, Kimura H, Itoh S. In vivo proton magnetic resonance spectroscopy study on premature ageing in adult Down's syndrome. Biol Psychiatry 1993; 34: 290-297.

Murphy DGM, DeCarli CD, Schapiro MB, Rapoport SI; Horwitz B. Age related differences subcortical nuclei, brain matter and cerebrospinal fluid in healthy men as measured with MRI. Arch Neurol 1992; 49: 839-849.

Murphy DGM, DeCarli CD, Daly E, Haxby JV, Allen G, White BJ, McIntosh AR, Powell CM, Horwitz B, Rapoport SI. X chromosome effects on female brain: a magnetic resonance imaging study of Turner's syndrome. Lancet 1993a; 342: 1197-1200.

Murphy DGM, DeCarli CD, Daly E, Gillette JA, McIntosh AR, Haxby JV, Teichberg D, Schapiro MB, Rapoport SI, Horwitz B. Volumetric magnetic resonance imaging in men with dementia of Alzheimer type: correlations with disease severity. Biol Psychiatry 1993b; 34: 612-621.

Naslund J, Haroutunian V, Mohs R, Davis KL, Davies P, Greengard P, Buxbaum JD. Correlation between elevated levels of amyloid β-peptide in the brain and cognitive decline. JAMA 2000; 283: 1571-1577.

National Institute for Health and Clinical Excellence. Dementia: supporting people with dementia and their carers in health and social care. NICE Clinical Guidance 42. Developed by the National Collaborating Centre for Mental Health, 2006.

Najlerahim A, Bowen D. Biochemical measurements in Alzheimer's disease reveal a necessity for improved neuroimaging techniques to study metabolism. Biochem J 1988; 251: 305-308.

Nieuwenhuis-Mark RE. Diagnosing Alzheimer's dementia in Down syndrome: problems and possible solutions. Res Devel Dis 2009; 30: 827-838.

Nishizuka Y. The molecular heterogeneity of protein kinase C and its implications for cellular regulation. Nature 1988; 334: 661-665.

Nitsch RM, Blusztajn JK, Pittas AG, Slack BE, Growdon JH, Wurtman RJ. Evidence for a membrane defect in Alzheimer disease brain. Proc Natl Acad Sci USA 1992; 89: 1671-1675.

O'Brien JT, Eagger S, Syed GMS, Sahakian BJ, Levy B. A study of regional cerebral blood flow and cognitive performance in Alzheimer's disease. J Neurol Neurosurg Psychiatry 1992; 55: 1182-1187.

Oliver C, Holland AJ. Down's syndrome and Alzheimer's disease: a review. Psychol Med 1986; 16: 307-322.

Oliver C. Perspectives on assessment and evaluation, in MP Janicki & AJ Dalton (eds) Dementia, Ageing and Intellectual Disabilities: A handbook. Philadelphia: Taylor and Francis/Bruner/Mazel 1999.

Pantel J, O'Leary DS, Cretsinger K, Bockholt HJ, Keefe H, Magnotta VA, Andreasen NC. A new method for the in vivo volumetric measurement of the human hippocampus with high neuroanatomical accuracy. Hippocampus 2001; 10: 752-758.

Parnetti L, Tarducci R, Presciutti O, Lowenthal DT, Pippi M, Palumbo B, Gobbi G, Pelliccioli GP, Senin U. Proton magnetic resonance spectroscopy can differentiate Alzheimer's disease from normal aging. Mech Ageing Dev 1997; 97: 9-14.

Pearlson GD, Breiter SN, Aylward EH, Warren AC, Grygorcewicz M, Frangou S, Barta PE, Pulsifer MB. MRI brain changes in subjects with Down syndrome with and without dementia. Dev Med Child Neurol 1998; 40: 326-334.

Pearlson GD, Warren AC, Starkstein SE, Aylward EH, Kumar AJ, Chase GA, Folstein MF. Brain atrophy in 18 patients with Down syndrome: a CT study. Am J Neuroradiol 1990; 11: 811-816.

Pearlson GD, Harris GJ, Powers RE. Quantitative changes in mesial temporal volume, regional cerebral blood flow, and cognition in Alzheimer's disease. Arch Gen Psychiatry 1992; 49: 402-408.

Pearson RCA, Esiri MM, Hiorns RW. Anatomical correlates of the distribution of the pathological changes in the neocortex in Alzheimer disease. Proc Natl Acad Sci USA 1985; 82: 4531-4534.

Pennanen C, Kivipelto M, Tuomainen S, Hartikainen P, Hanninen T, Laakso MP, Hallikainen M, Vanhanen M, Nissinen A, Helkala EL, Vainio P, Vanninen R, Partanen K, Soininen H. Hippocampus and entorhinal cortex in mild cognitive impairment and early AD. Neurobiol Aging 2004; 25: 303-310.

Perry RD, Irving D, Blessed G, Fairbairn A, Perry EK. Senile dementia of Lewy Body type. J Neurol Sci 1990; 95: 110-139.

Petersen RC, Smith GE, Ivnik RJ, Tangalos EG. Memory function in very early Alzheimer's disease. Neurology 1994; 44: 867-872.

Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999; 56: 303-308.

Petersen RC. Conceptual overview. In: Petersen RC. Mild Cognitive Impairment: Aging to Alzheimer's Disease. 1-14. New York, NY: Oxford University Press, 2003.

Petersen RC, Knopman D, Boeve BF. Role of hippocampal volumes in predicting progression to mild cognitive impairment. Neurology 2005; 64: 126-127.

Petrovitch H, White LR, Ross GW, Steinhorn SC, Li CY, Masaki KH, Davis DG, Nelson J, Hardman J, Curb JD, Blanchette PL, Launer LJ, Yano K, Markesbery WR. Accuracy of clinical criteria for AD in the Honolulu–Asia Aging Study, a population-based study. Neurology 2001; 57: 226–34.

Pfefferbaum A, Adalsteinsson E, Spielman D, Sullivan EV, Lim KO. In vivo spectroscopic quantification of the N-acetyl moiety, creatine, and choline from large volumes of brain gray and white matter: effects of normal aging. Magn Reson Med 1999; 41: 276-284.

Pinter JD, Brown WE, Eliez S, Schmitt JE, Capone GT, Reiss AL. Amygdala and hippocampal volumes in children with Down Syndrome: a high-resolution MRI study, Neurology 2001; 56: 972-974.

Pioro EP. MR spectroscopy in amyotrophic lateral sclerosis/motor neuron disease. J Neurol Sci 1997; 152 (suppl 1): 49-53.

Pitas RE, Boyles JK, Lee SH, Hui D, Weisgraber KH. Lipoproteins and their receptors in the central nervous system. Characterization of the lipoproteins in cerebrospinal fluid and identification of apolipoprotein B, E (LDL) receptors in the brain. J Biol Chem 1987; 262: 14352-14360.

Prasher VP, Chowdhury TA, Rowe BR, Bain SC. ApoE genotype and Alzheimer's disease in adults with Down syndrome: meta-analysis. Am J Ment Retard 1997; 102: 103-110.

Prasher VP, Farrer MJ, Kessling AM, Fisher EM, West RJ, Barber PC, Butler AC. Molecular mapping of Alzheimer-type dementia in Down's syndrome. Ann Neurol 1998; 43: 380-383.

Prasher V, Cumella S, Natarajan K, Rolfe E, Shah S, Haque MS. Magnetic resonance imaging, Down's syndrome and Alzheimer's disease: research and clinical implications. JIDR 2003; 47: 90-100.

Prince M, Acosta D, Albanese E, Arizaga R, Ferri CP, Guerra M, Huang Y, Jacob KS, Jimenez-Velazquez IZ, Rodriguez JL, Salas A, Sosa AL, Sousa R, Uwakwe R, van der Poel R, Williams J, Wortmann M. Ageing and dementia in low and middle income countries – using research to engage with public and policy makers. Int Rev Psychiatry 2008; 20: 332-343.

Raber J, Wong D, Buttini M, Orth M, Bellosta S, Pitas RE, Mahley RW, Mucke L. Isoform-specific effects of human apolipoprotein E on brain function revealed in ApoE knockout mice: increased susceptibility of females. Proc Natl Acad Sci USA 1998; 95: 10914-10919.

Raber J, Wong D, Yu GQ, Buttini M, Mahley RW, Pitas RE, Mucke L. Apolipoprotein E and cognitive performance. Nature 2000; 404: 352-354.

Rajanayagam V, Balthazor M, Shapiro EG, Krivit W, Lockman L, Stillman AE. Proton MR spectroscopy and neuropsychological testing in adrenoleukodystrophy. Am J Neuroradiol 1997; 18: 1909-1914.

Rasmusson DX, Carson KA, Brookmeyer R, Kawas C, Brandt J. Predicting rate of cognitive decline in probable Alzheimer's disease. Brain Cogn 1996; 31: 133-147.

Raz N, Torres IJ, Briggs SD, Spencer WD, Thornton AE, Loken WJ, Gunning FM, McQuain JD, Driesen NR, Acker JD. Selective neuroanatomic abnormalities in Down's syndrome and their cognitive correlates: evidence from MRI morphometry. Neurology 1995; 45: 356-366

Raz N, Gunning-Dixon FM, Head DP, Dupuis JH, Acker JD. Neuroanatomical correlates of cognitive aging: evidence from structural MRI. Neuropsychology 1998; 12: 95-114.

Reiman EM, Caselli RJ, Yun LS, Chen K, Brandy D, Minoshima S, Thibodeau SN, Osbourne D. Preclinical evidence of Alzheimer's disease in persons homozygous for the ε4 allele for apolipoprotein E. N Engl J Med 1996; 334: 752-758.

Reiman EM, Uecker A, Caselli RJ, Lewis S, Bandy D, de Leon MJ, De Santi S, Convit A, Osborne D, Weaver A, Thibodeau SN. Hippocampal volumes in cognitively normal persons at genetic risk for Alzheimer's disease. Ann Neurol 1998; 44: 288-291.

Reiss AL, Lee J. Freund L. Neuroanatomy of fragile X syndrome. Neurology 1994; 44: 1317.

Report of the Working Party on Services for the Elderly. The Years Ahead: A Policy for the Elderly. Dublin: Stationery Office 1988.

Reynolds GP, Warner CEJ. Amino acid neurotransmitter deficits in adult Down's syndrome brain tissue. Neurosci Lett 1988; 94: 224-227.

Ridha BH, Anderson VM, Barnes J, Boyes RG, Price SL, Rossor MN, Whitwell JL, Jenkins L, Black RS, Grundman M. Volumetric MRI and cognitive measures in Alzheimer disease: comparison of markers of progression. J. Neurol 2008; 255: 567-574.

Riekkinen P Jr, Kejonen K, Laakso MP, Soininen H, Partanen K, Riekkinen M. Hippocampal atrophy is related to impaired memory, but not frontal functions in non-demented Parkinson's disease patients. Neuroreport 1998; 9: 1507-1511.

Roberts GW, Nash M, Ince PG, Royston MC, Gentleman SM. On the origin of Alzheimer's disease: a hypothesis. NeuroReport 1993; 4: 7-9.

Roberts N, Garden AS, Cruz-Orive LM, Whitehouse GH, Edwards RHT. Estimation of fetal volume by MRI and stereology. British J Radiology 1994; 67: 1067-1077.

Roberts N, Puddephat MJ, McNulty, V. The benefit of stereology for quantitative radiology. British J Radiology 2000; 73: 679-697.

Rocca WA, Van Duijn CM, Clayton D, Chandra V, Fratiglioni L, Graves AB, Heyman A, Jorn AF, Kokmen E, Kondo K, Mortimer JA, Shalat SL, Soininen H, Hofman A. Maternal age and Alzheimer's disease: a collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group. Int J Epidemiol 1991; 20 (suppl 2): 21-27.

Rodrigue KM & Raz N. Shrinkage of the entorhinal cortex over five years predicts memory performance in healthy adults. J Neuroscience 2004; 24: 956-963.

Rombouts S, Machielsen W, Witter M, Barkhof F, Lindeboom J, Scheltens P. Visual association encoding activates the medial temporal lobe: a functional magnetic resonance imaging study. Hippocampus 1997; 7: 594-601.

Rose SE, de-Zubicaray GI, Wang D, Galloway GJ, Eagle SC, Semple J, Doddrell DM. A $^{1}H$ MRS study of probable Alzheimer's disease and normal aging: implications for longitudinal monitoring of dementia progression. Magn Reson Imaging 1999; 17: 291-299.

Roth M, Huppert FA, Mountjoy CQ, Tym E. CAMDEX- Cambridge Examination for Mental Disorders of the Elderly. Cambridge University Press, 1998.

Rountree SD, Waring SC, Chan WC, Lupo PJ, Darby EJ, Doody RS. Importance of subtle amnestic and nonamnestic deficits in mild cognitive impairment: prognosis and conversion to dementia. Dement Geriatr Cogn Disord, 2007; 24: 476-482.

Rusinek H, Frid D, Tsui WH, Tarshish CY, Convit A, de Leon MJ. Regional brain atrophy rate predicts future cognitive decline: 6 year longitudinal MR imaging study of normal aging. Radiology 2003; 229: 691-696.

Rusinek H, Endo Y, De Santi S, Frid D, Tsui WH, Segal S, Convit A, de Leon MJ. Atrophy rate in medial temporal lobe during progression of Alzheimer's disease. Neurology 2004; 63: 2354-2359.

Scahill RI, Schott JM, Stevens JM, Rossor MN, Fox NC. Mapping the evolution of regional atrophy in Alzheimer's disease: unbiased analysis of fluid-registered serial MRI. Proc Natl Acad Sci USA 2002; 99: 4703-4707.

Scarmeas N, Albert SM, Manly JJ, Stern Y. Education and rates of cognitive decline in incident Alzheimer's disease. J Neurol Neurosurg Psychiatry 2006; 77: 308-316.

Schapiro MB, Luxenburg JS, Kaye JA, Haxby JV, Friedland RP, Rapoport SI. Serial quantitative CT analysis of brain morphometrics in adult Down's syndrome at different ages. Neurology 1989; 39: 1349-1353.

Schapiro MB, Haxby JV, Grady CL. Nature of mental retardation and dementia in Down syndrome: study with PET, CT and neuropsychology. Neurobiol Aging 1992; 13: 723-734.

Scheltens P. Early diagnosis of dementia: neuroimaging. J Neurol 1999; 246: 16-20.

Schmidt H, Schmidt R, Fazekas F, Semmler J, Kapeller P, Reinhart B, Kostner GM. Apolipoprotein E e4 allele in the normal elderly: neuropsychologic and brain MRI correlates. Clin. Genet 1996; 50: 293-299.

Schott JM, Fox NC, Frost C, Scahill RI, Janssen JC, Chan D, Jenkins R, Rossor MN. Assessing the onset of structural change in familial Alzheimer's disease. Ann Neurol, 2003; 53: 181-188.

Schott JM, Crutch SJ, Frost C, Warrington EK, Rossor MN, Fox NC. Neuropsychological correlates of whole brain atrophy in Alzheimer's disease. Neuropsychologia 2008; 46: 1732-1737.

Schuchmann S, Muller W, Heinemann U. Altered Ca2+ signalling and mitochondrial deficiencies in hippocampal neurons of trisomy 16 mice: a model of Down's syndrome. J Neurosci 1998; 18: 7216-7231.

Schuff N, Amend D, Ezekiel F, Steinman SK, Tanabe J, Norman D, Jagust W, Kramer JH, Mastrianni JA, Fein G, Weiner MW. Changes of hippocampal N-acetyl

aspartate and volume in Alzheimer's disease. A proton MR spectroscopic imaging and MRI study. Neurology 1997; 49: 1513-1521.

Schuff N, Amend DL, Meyerhoff DJ, Tanabe JL, Norman D, Fein G, Weiner MW. Alzheimer disease: quantitative H-1 MR spectroscopic imaging of frontoparietal brain. Radiology 1998; 207: 91-102.

Schuff N, Capizzano AA, Du AT, Amend DL, O'Neill J, Norman D, Kramer J, Jagust W, Miller B, Wolkowitz OM, Yaffe J, Weiner MW. Selective reduction of N-acetylaspartate in medial temporal and parietal lobes in AD. Neurology 2002; 58: 928-935.

Schumann CM, Hamstra J, Goodlin-Jones BL, Lotspeich LJ, Kwon, H, Buonocore MH, LAmmers CR, Reiss AL, Amaral DG The amygdala is enlarged in children but not adolescents with autism; the hippocampus is enlarged at all ages. J Neuroscience 2004; 24: 6392-6401.

Seab JB, Jagust WJ, Wong STS, Roos MS, Reed BR, Budinger TF. Quantitative NMR measurements of hippocampal atrophy in Alzheimer's disease. Magn Reson Med 1988; 8: 200-208.

Segonne F, Dale A, Busa E, Glessner M, Salvolini U, Hahn H, Fischl B, A hybrid approach to the skull-stripping problem in MRI, Neuroimage 2004; 22: 1060-1075.

Seidl R, Cairns N, Singewald, Kaehler ST, Lubec G. Differences between GABA levels in Alzheimer's disease and Down syndrome with Alzheimer-like neuropathology. Naunyn-Schmiedeberg's Arch Pharmacol 2001; 363: 139-145.

Selkoe DJ. Translating cell biology into therapeutic advances in Alzheimer's disease. Nature 1999; 399: 23-31.

Setern Y. What is cognitive reserve? Theory and research application of the reserve concept. J Int Neuropsychol Soc 2002; 8: 448-460.

Shonk TK, Moats RA, Gifford P, Michaelis T, Mandigo JC, Izumi J, Ross BD. Probable Alzheimer disease: diagnosis with proton MR spectroscopy. Radiology 1995; 195: 65-72.

Silbert LC, Quinn JF, Moore MM, Corbridge E, Ball MJ, Murdoch G, Sexton G, Kaye JA. Changes in premorbid brain volume predict Alzheimer's disease pathology. Neurology, 2003; 61: 487-492.

Silverman JM, Ciresi G, Smith CJ, Marin DB, Schnaider-Beeri M. Arch Gen Psychiatry 2005; 62: 565-573.

Simchowicz T. Histologische studien uber die senile demenz. Hist histopath arb 1910; 4: 267.

Simmons A, Arridge SR, Barker GJ, Williams SC. Simulation of MRI cluster plots and application to neurological segmentation. Magn Reson Imaging 1996; 14: 73-92.

Sluimer JD, van der Flier WM, Karas GB, Fox NC, Scheltens P, Barkhof F, Vrenken H. Whole-brain atrophy rate and cognitive decline: longitudinal MR study of memory clinic patients. Radiology 2008; 248: 590-598.

Sluimer JD, Bouwman FH, Vrenken H, Blankenstein MA, Barkhof F, van der Flier WM, Scheltens P. Whole-brain atrophy rate and CSF biomarker levels in MCI and AD: a longitudinal study. Neurobiol Aging 2010; 31: 758-764.

Small GW, Mazziotta JC, Collins MT, Baxter LR, Phelps ME, Mandelkern MA, Kaplan A, La Rue A, Adamson CF, Chang L, Guze BH, Corder EH, Saunders AM, Haines JL, Pericak-Vance MA, Roses AD. Apolipoprotein E type 4 allele and cerebral glucose metabolism in relatives at risk for familial Alzheimer disease. JAMA 1995; 273: 942-947.

Smigielska-Kuzia J & Sobaniec W. Brain metabolic profile obtained by proton magnetic resonance spectroscopy HMRS in children with Down syndrome. Adv Med Sci 2007; 52 (suppl 1): 183-187.

Smith AD, Jobst KA. Use of structural imaging to study the progression of Alzheimer's disease. British Medical Bulletin 1996; 52: 575-586.

Snowdon DA, Kemper SJ, Mortimer JA, Greiner LH, Wekstein DR, Markesbery WR. Linguistic ability in early life and cognitive function and Alzheimer's disease in late life. Findings from the Nun Study. J Am Med Assoc 1996; 21: 528-532.

Soininen HS, Partanen K, Pitkanen A, Vainio P, Hanninen T, Hallikainen M, Koivisto K, Riekkinen PJ. Volumetric MRI analysis of the amygdala and the hippocampus in subjects with age-associated memory impairment: correlation to visual and verbal memory. Neurology 1994; 44: 1660-1668.

Spillantini MG, Goedert M. Tau protein pathology in neurodegenerative diseases. Trends Neurosci 1998; 21: 428-433.

Squire LR, Zola-Morgan S. The medial temporal lobe memory system. Science, 1991; 20: 1380-1386.

St George-Hyslop PH. Piecing together Alzheimer's. Sci Am 2000; 283: 76-83.

Stern YP. Cognitive reserve and Alzheimer's disease. Alzheimer's Disease and Associated Disorders 2006; 20: 69-74.

Stokes CE, Hawthorne JN. Reduced phosphoinositide concentration in anterior temporal cortex of Alzheimer-diseased brains. J Neurochem 1987; 48: 1018-1021.

Storandt M, Hill R. Very mild senile dementia of the Alzheimer type-II Psychometric test performance. Arch Neurol 1989; 46: 383-386.

Stout JC, Jernigan TL, Archibald SL, Salmon DP. Association of dementia severity with cortical gray matter and abnormal white matter volumes in dementia of the Alzheimer type. Arch Neurol 1996; 53: 742-749.

Strauss E, Sherman EM, Spreen O. A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. Oxford University Press Inc, New York, 2006.

Sullivan E, March L, Mathalon DH, Lim KO, Pfefferbaum A. Age-related decline in MRI volumes of temporal lobe grey matter but not hippocampus. Neurobiol Aging 1995; 16: 591-606.

Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. Thieme, New York 1988.

Taoka T, Iwasaki S, Sakamoto M, Nakagawa H, Fukusumi A, Myochin K, Hirohashi S, Hoshida T, Kichikawa K. Diffusion anisotropy and diffusivity of white matter tracts within the temporal stem in Alzheimer disease: evaluation of the "tract of interest" by diffusion tensor tractography. AJNR Am J Neuroradiol 2006; 27: 1040-1045.

Temple V, Jozsvai E, Konstantareas MM, Hewitt TA. Alzheimer's dementia in Down's syndrome: the relevance of cognitive ability. J Intell Dis Res 2001; 45: 47-55.

Teipel SJ, Hampel H, Alexander GE, Schapiro MB, Horwitz B, Teichberg D, Daley E, Moller H-J, Hippius H, Rapoport SI. Dissociation between white matter pathology and corpus callosum atrophy in Alzheimer's disease. Neurlogy 1998; 51: 1381-1385.

Teipel SJ, Hampel H, Pietrini P, Alexander GE, Horwitz B, Daley E, Moller H-J, Schapiro MB, Rapoport SI. Region specific corpus callosum atrophy correlates with regional pattern of cortical glucose metabolism in Alzheimer's disease. Arch Neurol 1999; 56: 467-473.

Teipel SJ, Bayer W, Alexander GE, Zebuhr Y, Teichberg D, Kulic L, Schapiro MB, Moller HJ, Rapoport SI, Hampel H. Progression of corpus callosum atrophy in Alzheimer disease. Arch Neurol 2002; 59: 243-248.

Teipel SJ, Schapiro MB, Alexander GE, Krasuski JS, Horwitz B, Hoehne C, Moller HJ, Rapopport SI, Hampel H. Relation of corpus callosum and hippocampal size to age in nondemented adults with Down's syndrome. Am J Psychiatry 2003; 160: 1870-1878.

Teipel SJ, Alexander GE, Schapiro MC, Moller HJ, Rapoport SI, Hampel H. Age-related cortical grey matter reductions in non-demented Down's syndrome adults determined by MRI with voxel-based morphometry. Brain 2004; 127: 811-824.

Teri L, McCurry SM, Edland SD, Kukull WA, Larson EB. Cognitive decline in Alzheimer's disease: a longitudinal investigation of risk factors for accelerated decline. J Gerontol A Biol Sci Med Sci 1995; 50: 49-55.

Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, Hansen LA, Katzman R. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol 1991; 30: 572-580.

The 10/66 Dementia Research Group. Dementia in developing countries. A preliminary consensus statement from the 10/66 Dementia Research Group. Int J Geriat Psychiat 2000; 15: 14-20.

Thompson PM, Hayashi KM, de Zubicaray GI, Janke AL, Rose SE, Semple J, Hong MS, Herman DH, Gravano D, Doddrell DM, Toga AW. Mapping hippocampal and ventricular change in Alzheimer disease. Neuroimage 2004; 22: 1754-1766.

Tierney M, Szalai J, Snow W. Prediction of probable Alzheimer's disease in memory impaired patients. Neurology 1996; 46: 661-665.

Trivedi MA, Schmitz TW, Ries ML, Torgerson BM, Sager MA, Hermann BP, Asthana S, Johnson SC. Reduced hippocampal activation during episodic encoding in middle-aged individuals at genetic risk of Alzheimer's disease: a cross-sectional study. BMC Med 2006; 4: 1-14.

Turk V, Dodd K, Christmas M. Down's syndrome and dementia: Briefing for Commissioners. London: The Foundation for People with Learning Disabilities 2001.

Tyrrell J, Cosgrave M, McCarron M, McPherson J, Calvert J, Kelly A, McLaughlin M, gill M, Lawlor BA. Dementia in people with Down's syndrome. Int J Geriatr Psychiatry 2001; 16: 1168-1174.

Valenzuela MJ, Sachdev P. Magnetic resonance spectroscopy in AD. Neurology 2001; 56: 592-598.

Van der Flier WM, van Buchem MA, Weverling-Rijnsburger AWE, Mustsars ER, Bollen ELEM, Admiraal-Behloul F, Westendorp RGJ, Middlekoop HAM. Memory complaints in patients with normal cognition are associated with smaller hippocampal volumes. J Neurol 2004; 251: 671-675.

Van Dujin CM, Hofman A. Risk factors for Alzheimer's disease: the EURODEM collaborative re-analysis of case-control studies. Neuroepidemiology 1992: 11 (suppl 1): 106-113.

Van Hoesen GW, Solodkin A, Hyman BT. Neuroanatomy of Alzheimer's disease: hierachical vulnerability and neural system compromise. Neurobiol Aging 1995; 16: 278-280.

Visser FE, Aldenkamp AP, Huffelen AC, van Juilman M, Overweg J, van Wijk J. Prospective studies of the prevalence of Alzheimer-type dementia in institutionalized individuals with Down syndrome. Am J Ment Retard 1997; 101: 400-412.

Wardlaw JM, Marshall I, Wild J, Dennis MS, Cannon J, Lewis SC. Studies of acute ischemic stroke with proton magnetic resonance spectroscopy: relation between time from onset, neurological deficit, metabolite abnormalities in the infarct, blood flow, and clinical outcome. Stroke 1998; 29: 1618-1624.

White NS, Alkire MT, Haier RJ. A voxel-based morphometric study of nondemented adults with Down syndrome. Neuroimage 2003; 20: 393-403.

Whitehouse PJ, Price DL, Struble RG, Clark AW, Coyle JT, DeLong MR. Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. Science 1982; 215: 1237-1239.

Whitwell JL, Sampson EL, Watt HC, Harvey RJ, Rossor MN, Fox NC. A volumetric magnetic resonance imaging study of the amygdala in frontotemporal lobar degeneration and Alzheimer's disease. Dement Geriatr Cogn Disord 2005; 20: 238-244.

Wilcock GK, Esiri MM, Bowen DM, Smith CCT. Alzheimer's disease: correlation of cortical choline acetyltransferase activity with the severity of dementia and histological abnormalities. J Neurol Sci 1982; 57: 407-417.

Wilson RS, Li Y, Aggarwal NT, Barnes LL, McCann JJ, Gilley DW, Evans DA. Education and the course of cognitive decline in Alzheimer disease. Neurology 2004; 63: 1198-1202.

Wisniewski KE, Dalton AJ, McLachlan C, Wen GY, Wisniewski HM. Alzheimer's disease in Down's syndrome: clinicopathologic studies. Neurology 1985; 35: 957-961.

Wisniewski KE. Down syndrome children often have brain with maturation delay, retardation of growth, and cortical dysgenesis. Am J Med Genet 1990; 7: 274-281.

World Health Organization. World Health Report 2003 – Shaping the future. Geneva: WHO 2003.

World Health Organisation Website. Definition: intellectual disability. http://www.euro.who.int/en/what-we-do/health-topics/noncommunicable-diseases/mental-health/news/news/2010/15/childrens-right-to-family-life/definition-intellectual-disability

Wurtman RJBJ, Marie JC. Autocannibalism of choline-containing membrane phospholipids in the pathogenesis of Alzheimer's disease. Neurochem Int 1985; 7: 369-372.

Xu Y, Jack CR Jr, O'Brien PC, Kokmen E, Smith GE, Ivnik RJ, Boeve BF, Tangalos RG, Petersen RC. Usefulness of MRI measures of entorhinal cortex versus hippocampus in AD. Neurology 2000; 54: 1760-1767.

Yamauchi H, Fukuyama H, Harada K, Nabatame H, Ogawa M, Ouchi Y, Kimura J, Konishi J. Callosal atrophy parallels decreased cortical oxygen metabolism and neuropsychological impairment in Alzheimer's disease. Arch Neurol 1993; 50: 1070-1074.

Yamaguchi S, Meguro K, Shimada M, Ishizaki J, Yamadori A, Sekita Y. Five year retrospective changes in hippocampal atrophy and cognitive screening test performances in very mild Alzheimer's disease: the Tajiri project. Neuroradiology 2002; 44: 43-48.

Yao FS, Caserta MT, Wyrwicz AM. In vitro 1H and 31P NMR spectroscopic evidence of multiple aberrant biochemical pathways in murine trisomy 16 brain development. Int J Dev Neurosci 2000; 18: 833-841.

Yavuz BB. Hippocampal volumetry in Alzheimer's disease, vascular dementia, mild cognitive impairment and normal cognitive status groups of geriatric age. Thesis in Internal Medicine, Hacettepe University Medical Faculty, Ankara 2004.

Young LT, Kish SJ, Li PP. Decreased brain [$^3$H] inositol 1,4,5-triphosphate binding in Alzheimer's disease. Neurosci Lett 1988; 94: 198-202.

Zakzanis KK. Quantitative evidence for neuroanatomic and neuropsychological markers in dementia of the Alzheimer's type. J Clin Exp Neuropsychol 1998; 20: 259-269.

Zamrini E, De Santi S, Tolar M. Imaging is superior to cognitive testing for early diagnosis of Alzheimer's disease. Neurobiol Aging 2004; 25: 685-691.

Zhu X, Schuff N, Kornak J, Soher B, Yaffe K, Kramer JH, Ezekiel F, Miller BL, Jagust WJ, Weiner MW. Effects of Alzheimer disease on fronto-parietal brain N-

acetyl aspartate and myo-inositol using magnetic resonance spectroscopic imaging. Alzheimer Dis Assoc Disord 2006; 20: 77-85.

Zigman W, Silverman W, Wisniewski HM. Aging and Alzheimer's disease in Down syndrome: clinical and pathological changes. Ment Retard Dev Disabil Res Rev 1996; 2: 73-79.

Zola-Morgan S, Squire LR, Amaral EG, Suzuki WA. Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment, J Neurosci 1989; 9: 4355-4370.