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A longitudinal study of magnetic resonance imaging (MRI) and psychometric measures as predictors of cognitive decline in symptomatic individuals without evidence of deficits.

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Hilary Anne Archer

University College London
Institute of Neurology

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ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

Declaration Statement

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

Hilary Archer

Abstract

Thirty-five subjects with symptoms of memory loss but no cognitive impairment (SNCI), and 21 subjects with mild cognitive impairment (MCI) were followed for two years, along with 30 age and sex matched healthy volunteers. Each subject underwent annual clinical and neuropsychological assessment and magnetic resonance imaging (MRI) brain scans. The serial neuroimaging and neuropsychological assessments were assessed to determine whether change in either measure was associated with a diagnosis of MCI or AD at 2 years. A disease severity rating (Clinical Dementia Rating) was used as a secondary outcome measure.

Baseline characteristics of the three cohorts showed that the MCI could be well differentiated on neuropsychological performance and neuroimaging measures from the SNCI and control cohorts. Aspects from the clinical history, including informant rating and use of memory aids, also showed an association with baseline neuropsychological performance in those with memory symptoms.

After two years of follow-up, the annual rate of conversion to MCI or AD in the SNCI group was 6%. Conversion to AD among the MCI subjects was 15%. Increased rates of cerebral atrophy over one year were found in the MCI group as compared to the control and SNCI groups. Additionally, rates of cerebral atrophy over one year were higher in those SNCI patients who converted to a diagnosis of MCI or AD at two years, than in those who remained stable. Neuropsychological measures were also informative, with MCI patients performing differently over one year compared to those in the SNCI and control groups, while within the SNCI group measures of poor memory performance were consistently associated with cognitive decline at 2 years.

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Glossary

6dof	Six degrees of freedom
9dof	Nine degrees of freedom
11C-PIB	Pittsburgh compound C
AchEI	Acetylcholinesterase
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's disease assessment scale-cognitive subscale
ADRDA	Alzheimer's disease and related disorders association
AIDS	Acquired immune deficiency syndrome
aMCI	Amnestic mild cognitive impairment
ApoE	Apolipoprotein E
APP	Amyloid precursor protein
BBSI	Brain boundary shift integral
BMI	Body mass index
CAS	Clinical anxiety scale
CDR	Clinical dementia rating
CERAD	Consortium to establish a registry for Alzheimer's disease
CIBIC-Plus	Clinician interview-based impression of change plus caregiver input
CSF	Cerebrospinal fluid
CT	Computerized tomography
CVLT	Californian verbal learning test
DLB	Dementia with Lewy bodies
DSM-IV	Diagnostic and statistical manual of mental disorders – 4^{th} edition
EC	Entorhinal Cortex
ECG	Electrocardiogram
EEG	Electroencephalogram
EFT	Embedded figure test
FAD	Familial Alzheimer's Disease
fMRI	Functional magnetic resonance imaging
FLAIR	Fluid attenuation inversion recovery
FTD	Frontotemporal Dementia
FTLD	Frontotemporal lobar degeneration
GE	General Electric
GDS	Geriatric depression scale

GNT	Graded naming test
GRASS	Gradient recalled acquisition at steady state
HIV	Human immunodeficiency virus
MCI	Mild cognitive impairment
MIDAS	Medical information display and analysis system
MMSE	Mini-mental state examination
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MTL	Medial temporal lobe
NART	National adult reading test
NFT	Neurofibrillary tangle
NIA	National institute for ageing
NINCDS	National institute of neurological and communicative disorders and stroke
PALT	Paired associates learning test
PET	Positron emission tomography
PS1	Presenilin 1 gene
PS2	Presenilin 2 gene
RF	Radiofrequency
RMT	Recognition memory test
ROF	Rey-Osterreith figure
ROI	Region of interest
SD	Standard deviation
SNCI	Symptoms no cognitive impairment
SNR	Signal-to-noise ratio
SPECT	Single photon emission computed tomography
SPM	Statistical Parametric Mapping, the software package used for statistical analysis of structural and functional images
T	Tesla
TE	Time to echo i.e. time between transmission of RF pulse and collection of signal
TIV	Total intracranial volume
TMT	Trail making test
TR	Time to repeat i.e. time between RF pulses

VBM Voxel-based morphometry, the application of SPM to highlight grey matter differences between groups, based on structural MRIs

VD Vascular Dementia

VOSP Visual and object space perception

WAIS Wechsler adult intelligence scale

WASI Wechsler abbreviated scale of intelligence

The problem

Alzheimer's disease (AD) is the commonest cause of dementia within the United Kingdom, increasing in prevalence with age of the population. As our populations continue to age over the next decades, the prevalence of AD will escalate further. This increasing disease burden will inevitably result in pressure on families and community structures and significantly increase the need for extended health and social service support.

Symptomatic treatments for Alzheimer's disease can now be prescribed. Recent advances in the field of therapeutics suggest that drugs with the potential to modify the effects of the disease may soon also become available. With trials of these drugs currently underway it is essential to have robust techniques at hand to identify those individuals who will benefit from treatment.

In the absence of a screening test, individuals with AD are currently identified following referral by the patient himself or by a family member to the health services. A diagnosis of 'probable' AD relies on a clinical history, cognitive performance on neuropsychological tests and brain appearance on MRI or CT that are suggestive of this diagnosis. Once given this diagnosis a patient can then be started on treatment.

However, once an individual has profound memory impairment and a change in cerebral structure consistent with AD, significant, irreversible brain cell loss has already taken place. The first changes in the brain due to AD can take place as many as 20 years prior to diagnosis. Therefore the challenge is to identify individuals in the early stages of AD before substantial brain cell loss has taken place. Treatment of this patient group would maximise the effects of disease modifying therapies.

Identification of individuals with early AD is problematic. Although symptoms of memory loss are one of the first signs of AD, they are also associated with psychiatric illnesses such as depression or anxiety, can result from systemic illness or cerebrovascular disease, or may simply be the result of normal ageing. Similarly, interpretation of neuropsychological assessments and neuroimaging are confounded by

the wide variation in normal scores and brain appearance within the general population. Psychiatric illness can result in impaired cognition and poor neuropsychology test results, and there is often significant overlap between the early changes seen on magnetic resonance imaging in AD with other neurodegenerative diseases.

The aim of this thesis is to examine whether symptoms of memory loss, cognitive performance and brain appearance over time could be used to predict future cognitive decline and identify individuals in the very early stages of AD.
I have endeavoured (1) to assess whether symptoms of memory impairment in a clinical setting predict future cognitive impairment, (2) to assess the relative merits of history taking, neuropsychological assessment and neuroimaging in prediction of future cognitive impairment, (3) to provide clinically useful information for those referring patients to and working in memory clinics for example, on whether to initiate treatment or not and how to plan patient follow up, (4) to assess the clinical utility of annual neuropsychological assessments and neuroimaging in the follow up of these individuals and (5) to ascertain the outcome of patients referred to memory clinics who have no memory impairment at presentation.

To achieve this I have followed a group of individuals who have presented to clinical services with memory complaints and gathered detailed clinical information about them, as well as compiled annual neuropsychological assessments and neuroimaging records over a two-year period.

Introduction

1. Alzheimer's disease

1.1. Epidemiology of dementia and AD

Dementia is a clinical term used to describe the progressive impairment of multiple cognitive domains (e.g., memory, judgement, naming) associated with a decline in day-to-day functioning in the absence of impaired consciousness. It is one of the most important causes of disability in the elderly, involving as many as 10% of those over 65 years of age(Knopman et al. 2001). An estimated 4.624 million Europeans between 30 and 99 years of age suffered from different types of dementias in 2000 (12.3 per 1 000 inhabitants). The most common causes were Alzheimer's disease (about 50-70% of cases) and vascular dementia (about 30%); other primary causes include Fronto-temporal Lobar Degeneration, Lewy Body dementia and Prion disease. As life expectancy increases the incidence of dementia is also increasing and statistical projections suggest that our populations will continue to age. In 2000, 15% of the population in Europe was aged over 65 and nearly 3% over 80. By 2030 it is thought that these numbers will increase to 24% and 6% respectively(Kinsella and Phillips 2005).

Alzheimer's disease is the most common cause of dementia in the United Kingdom affecting over 5% of the population above 65 years(Moliner AM et al. 2002). The expected rise in prevalence of AD over the next 30 years and the resulting socioeconomic burden of necessary health care provision and social support is of serious and growing concern.

1.2. Clinical presentation of AD

Alzheimer's disease is a progressive neurodegenerative disease which most commonly presents with symptoms of memory loss. Patients may find that they have difficulty remembering conversations or events that have taken place whilst companions may

notice they are more repetitive in their conversation. As the disease progresses, deficits in memory are characteristically joined by impaired executive functioning and reasoning, followed by naming difficulties and, later, the appearance of visuospatial and visuoperceptive impairments (Lambon Ralph et al. 2003). This course can be variable, and variants with atypical manifestations have been described(Galton et al. 2000). The average disease duration from diagnosis depends on age at diagnosis, with a median life span of 7-10 years for those in their 60s and early 70s, to only about 3 years or less for patients whose conditions are diagnosed when they are 90 years of age and older (Brookmeyer et al. 2002).

1.3. Diagnostic criteria for AD

A diagnosis of 'definite' AD can only be given where there is histopathological evidence of the disease process. This is most commonly demonstrated at post mortem examination. A diagnosis of 'probable' AD is therefore given in the clinical setting according to certain criteria. The most widely used of these are the DSM-IV (from the fourth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders) (DSM-IV 1994), and the NINCDS/ADRDA (from the joint task force of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association)(McKhann et al. 1984). To fulfill these criteria there must be a progressive worsening of memory and other cognitive functions with deficits in two or more areas of cognition such as language, orientation or executive functioning. These deficits must be in the absence of a disturbance of consciousness or other systemic disorders or brain diseases that could account for this disturbance in function. Support for the diagnosis comes from a positive family history for AD and impaired activities of daily living (see Appendices 1 and 2 for full definitions). Using these criteria it has been found that a diagnosis of "probable" AD achieves a sensitivity of 81% with a specificity of 70%. These figures reflect the fact that there is an overlap between several clinical features of AD and of non-AD dementias (Knopman et al. 2001).

1.4. Histopathological diagnosis of AD

A diagnosis of 'definite' Alzheimer's disease is based upon the finding of neurofibrillary tangles (NFTs), neuropil threads, extracellular β-amyloid protein and neuritic plaques in brain tissue. A diagnosis is given dependant on the extent and distribution of these changes. As with the clinical diagnosis of AD, there are several ways of rating these histopathological changes. They include the Braak and Braak classification (Braak and Braak 1991), the consortium to establish a registry for Alzheimer's disease (CERAD) criteria (Mirra et al. 1991), the National Institute of Aging criteria (Khachaturian 1985) and the National Institute on Aging-Reagan Institute Criteria (Hyman and Trojanowski 1997). These ratings differ on whether they are based on the presence of neuritic plaques or NFTs and whether or not an age correction is applied. A good correlation has been shown between NIA-Reagan and NIA and CERAD criteria (Newell et al. 1999). With the association of these histopathological changes with AD, much research has sought to elucidate both the progression and aetiology of these changes.

1.5. Histopathology, progression and pathogenesis

AD is characterized neuropathologically by intracellular neurofibrillary tangles (NFTs) and extra-cellular amyloid plaques. These pathological changes are thought to begin in the entorhinal cortex and progress to involve the hippocampus before affecting the cortex more widely (Braak and Braak 1991).

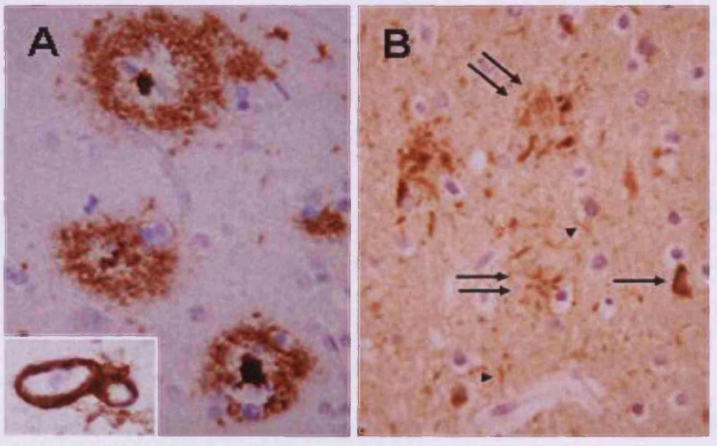


Figure 1-1Histopathology of AD

Aß-positive amyloid plaques (A) and tau-positive neurofibrillary tangles (arrow), neuropil threads (arrowhead) and plaque-associated abnormal neurites (double arrow) (B) in the temporal cortex. Insert on A illustrates the presence of deposition of Amyloid beta in blood vessels (cerebral amyloid angiopathy). A: Aß immunohistochemistry; B: tau immunohistochemistry. Photograph courtesy of Dr T Revesz and Dr J Holton of Queen Square Brain Bank, Institute of Neurology, University College London, London, UK.

NFTs are intraneuronal bundles of highly phosphorylated and aggregated Tau. In normal neurons Tau protein helps to stabilise the microtubule cytoskeleton essential for axonal transport. Abnormal Tau protein can also be found in other diseases such as Pick's disease, corticobasal degeneration and progressive supranuclear palsy.
The plaques are composed of insoluble beta-amyloid and are found closely associated with dystrophic neurons and dendrites, activated microglia and reactive astrocytes (see figure 1).

The formation of amyloid plaques is thought to occur following the abnormal cleavage of the amyloid precursor protein (APP). Sequential cleavage of APP by β and γ secretase results in formation of Amyloid-β-42, an insoluble protein and constituent of the amyloid plaque. Plaque build up is thought to incite an inflammatory response, leading to progressive disruption of neuronal and functional injury throughout the brain. The deposition of amyloid beta is thought by many to be central to the pathogenesis of AD and is known as the "amyloid cascade hypothesis"(Hardy and Higgins 1992) . This is supported by three main lines of evidence. Firstly, work in Trisomy-21 subjects has shown amyloid deposition to occur prior to abnormal phosphorylation of Tau proteins and up to 20 years prior to objective cognitive decline, therefore early in the disease process (Hyman 1992). Secondly, the gene mutations identified as causing familial AD control β-amyloid production (Citron et al. 1992). Thirdly, overexpression of human amyloid precursor protein (APP) or β-amyloid in transgenic mice leads to the neuropathological characteristics of AD (Games et al. 1995). However, exactly how amyloid plaques or other elements in the cascade are related to neuronal destruction is still unclear.

As a result of these pathological processes, biological changes occur in the brain on a microscopic level, including neurotransmitter loss, dendritic pruning of neurons and neuronal cell death. The consequence of these changes at a macroscopic level is brain atrophy.

1.6. Macroscopic changes in AD

In AD the progression of macroscopic changes mirrors the microscopic changes. These can be visualised at post mortem or *in vivo* using structural imaging techniques such as magnetic resonance imaging (MRI). Early in the disease process medial temporal lobe substructures such as the hippocampi, entorhinal cortex and amygdalae begin to atrophy. With disease progression the inferolateral regions of the temporal lobes and posterior cingulate, and then the frontal lobes become involved(Scahill et al. 2002). With this generalised atrophy the sulci begin to widen as cortical tissue is lost and the ventricles enlarge (see Figure 1-2). This pattern of progression can be used to help discriminate AD from other dementias such as frontotemporal lobar dementia which primarily affects the frontal and temporal cortices. The degree of cerebral atrophy visualised with MRI correlates with the pathological progression of the disease through the cortex (Bancher et al. 1993). Semi-quantitative measurement of such an atrophic pattern has been shown to be useful at discriminating AD from normal controls with a high sensitivity (87%) and high specificity (93%). These measures have also been correlated with memory scores (Scheltens et al. 1992). MRI scanning and neurodegenerative disease is discussed more fully in chapter 5.

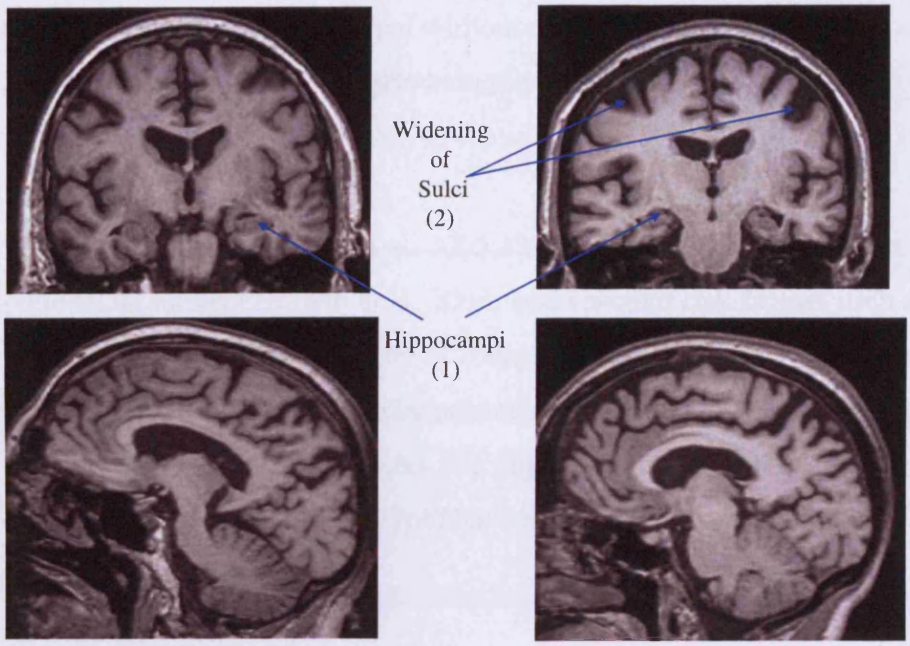


Figure 1-2: Coronal and sagittal views on MRI of a healthy control (A) and a subject with AD (B) demonstrating the characteristic macroscopic changes of AD, (1) atrophy of hippocampi with attendant temporal lobe atrophy and (2) with disease progression, global atrophy with expansion of cerebrospinal fluid spaces and sulcal widening.

1.7. Risk factors for development of AD

AD is known to be associated with different risk factors for its development, both genetic and environmental. Familial AD has a prevalence of less than 0.1%(Harvey et al. 2003), with a younger age of onset (before 65 years of age) and clear autosomal dominant inheritance of the disease process. Point mutations in three genes associated with amyloid processing, the amyloid precursor protein (APP) (on chromosome 21), presenilin 1 (PS1) (on chromosome 14) and presenilin 2 (PS2) (on chromosome 1) are known to be causative.

Other genetic factors are also important in the development of sporadic AD, which has a later age of onset (over 65 years of age), although the exact influence of these genes is uncertain. The Apolipoprotein E (ApoE) gene encodes a plasma-membrane protein

involved in lipid transport. Possession of the E4 allele of this gene is associated with an earlier age of disease onset (10-15 years earlier) in Europeans. An individual homozygous for the E4 allele is thought to have a risk three to four times greater of developing AD than that of an individual without this allele. Other genes on chromosomes 6, 9, 10, 12 and 19 are also being investigated for an association with the development of AD (Bird 2005).

Increased age, female gender (Heun et al. 2005;Kawas et al. 2000) , lower education and occupational attainment (Smyth et al. 2004) and vascular risk factors such as cholesterol, hypertension and diabetes(de la Torre 2002) have also been put forward as increasing the likelihood of developing late onset AD. Evidence of memory change in the form of subjective memory complaints and objective impairment of memory (Mild Cognitive Impairment of the amnestic type) have also been cited as risk factors and are the subject of the following chapters.

1.8. Treatments available and early intervention, memory aids

Much of the treatment given to those with AD is supportive. This takes the form of information from memory clinics and general practices on the use of different memory aids as well as the assessment of housing for aid installation, provision of help from carers or day care centers, and guidance in accessing the appropriate financial benefits. All these resources can greatly improve the quality of life of the patient and main carer.

To date, however, there are no disease-reversing medications and few that relieve symptoms. Anticholinesterase inhibitors form the main group of symptomatic treatments, with their mode of action thought to involve raising acetylcholine levels in the brain, countering the degeneration of cholinergic basal forebrain neurons innervating the cortex. These drugs have been shown to produce small improvements in cognition and activities of daily living in mild to moderate AD. However a reduction in rate of institutionalization or progress of disability has not always been seen (Courtney et al. 2004).

Anti-inflammatory drugs, vitamins, hormone replacement therapy, statins and herbal supplements have also been investigated for symptomatic or disease reversing effects, however none of these treatments has so far been shown to be effective.

With deposition of β-amyloid proposed to be central to the development of AD one promising disease reversing strategy is to use the immune system to eliminate excess β amyloid from the brain. Aβ deposition can be prevented or ameliorated in βAPP-transgenic mice by active immunization with the Aβ peptide. Active immunization in humans with Aβ-42 has recently been carried out, but development of aseptic meningoencephalitis in 6%, resulted in termination of the trial. However available data suggested that in those AD subjects who mounted an antibody response there were signs of clinical benefit, with evidence of Aβ clearance from some brain regions at post mortem examination (Nicoll et al. 2003). Studies using passive immunization are now underway.

With the current interest surrounding the development of disease modifying therapies for AD, it has become of great importance to identify individuals at the earliest stage of the disease process possible so that treatments may be started at a time when they will have most benefit. This 'pre-AD' stage is termed 'mild cognitive impairment' and will form the subject of the next chapter.

2. Mild cognitive impairment (MCI)

2.1. Definition

The term Amnestic Mild Cognitive Impairment (aMCI) has been utilised by Petersen et al (Petersen et al. 2001) to describe the phase prior to Alzheimer's disease where cognitive impairment has been shown to exist but not of a severity consistent with a diagnosis of dementia. As such it has come to be regarded as a transition phase between normal ageing and AD (figure 1).

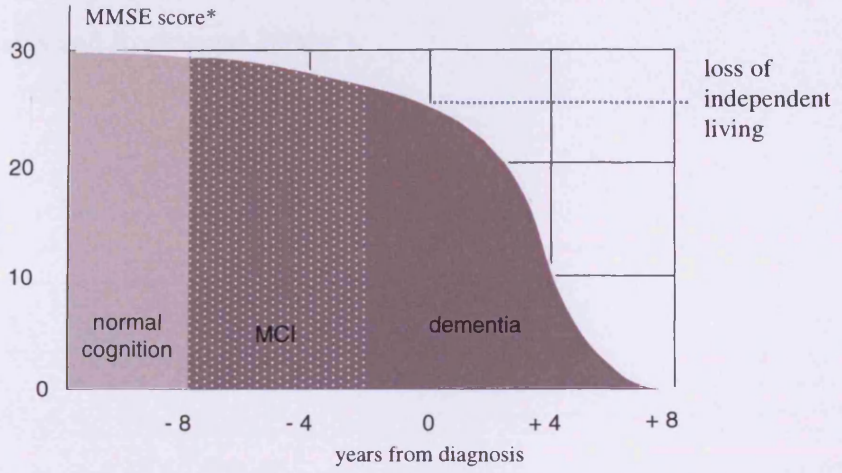


Figure 2-1 MCI as a transitional phase between normal ageing and dementia.

*** Mini-mental state examination**

2.2. History and classification

Attempts to characterise cognitive impairment associated with ageing began as early as 1962, with Kral et al coining the term 'Benign Senescent Forgetfulness' (BSF). BSF described the occasional inability to recall relatively unimportant parts of experiences of the past (Kral VA 1962). Unlike aMCI, BSF was thought to represent an age related problem and therefore part of a normal ageing continuum of cognition. This was taken

further by Crook et al in 1986 with the introduction of the term 'Age Associated Memory Impairment (AAMI)(Crook T et al. 1986). This criteria required gradual onset memory impairment in individuals over a certain age to be substantiated by neuropsychological testing (age $\geq$50 and performance on cognitive tests 1SD below the mean test value of younger adults). This was later modifed by Blackford and La Rue, with the addition of an upper age limit of 79 years and the requirement for preserved general intelligence. In addition to AAMI, they defined two other categories of memory loss, age-consistent memory impairment (ACMI) and late –life forgetfulness (LLF) (Blackford RC and La Rue A 1989). Other groups have moved away from an isolated deficit in memory impairment, hoping to focus more broadly on cognitive decline. Levy in 1994 incorporated this approach in his definition of ageing-associated cognitive decline (AACD)(Levy 1994). Here, cognitive impairment was age standardized and could include difficulty with memory, learning, attention, concentration, thinking, language or visuospatial functioning. Table 2-1 gives an overview of the most commonly used definitions of cognitive impairment (for review see Davis HS et al 2004 (Davis and Rockwood 2004)).

Table 2-1 Cognitive impairment syndromes

Adapted from de Carli et al 2003 (DeCarli 2003)

Term	Source	Diagnostic Criteria
Benign senescent forgetfulness (BSF)	Kral 1964	Memory complaints
Age-associated memory impairment (AAMI)	Crook 1986	Subjective and objective memory impairment
Late-life forgetfulness (LLF)	Blackford and La Rue 1989	AAMI and age-adjusted deficits in ≥4 cognitive tests
Mild cognitive decline	ICD-10 1993(WHO 1993)	Impaired on tests of memory learning, memory/concentration secondary to defined illness
Aging-associated cognitive decline (AACD)	Levy 1994	Age-adjusted impairment on any cognitive task
Age-related cognitive decline (ARCD)	DSM-IV 1994 (DSM-IV 1994)	Objective decline in cognitive function
Mild neurocognitive decline	DSM-IV 1994	Impairments in memory learning, perceptual-motor,linguistic, or executive functioning
Amnestic mild cognitive impairment (aMCI)	Petersen 1995	Subjective memory complaint, objective memory impairment adjusted for age and education with no dementia.
Cognitive impairment-no dementia (CIND)	Graham 1997	Impairments in memory, learning, perceptual-motor, linguistic or executive functioning in the absence of clinically defined dementia.

The previous terms described the spectrum of cognitive performance thought to occur with ageing. However others have viewed these impairments not as benign, but as part of a disease continuum towards dementia. The term Cognitive Impairment, No Dementia (CIND) (Ebly et al. 1995;Graham et al. 1997) was designed to encompass a variety of conditions which while giving rise to cognitive impairment, did not fulfil

criteria for dementia. The term 'Mild Cognitive Impairment' (MCI), first proposed by Flicker and used with modifications by Petersen, was formulated to identify individuals with cognitive impairment who were at high risk of developing dementia.

2.3. Mild cognitive impairment

Mild cognitive impairment was initially defined as the presence of subjective memory complaints, normal activities of daily living, no dementia, and impairment of one cognitive domain but normal general cognitive functioning (Flicker et al. 1991;Petersen et al. 1995). These criteria were later modified to reflect an AD prodrome with the objective cognitive impairment criterion narrowed to just objective memory impairment. This MCI sub group was named amnestic mild cognitive impairment. MCI with impairment of a single non memory domain and MCI with slight impairment in multiple domains have also been proposed (Petersen 2004). Figure 2-2 summarizes the other types of MCI and their likely resultant pathological states.

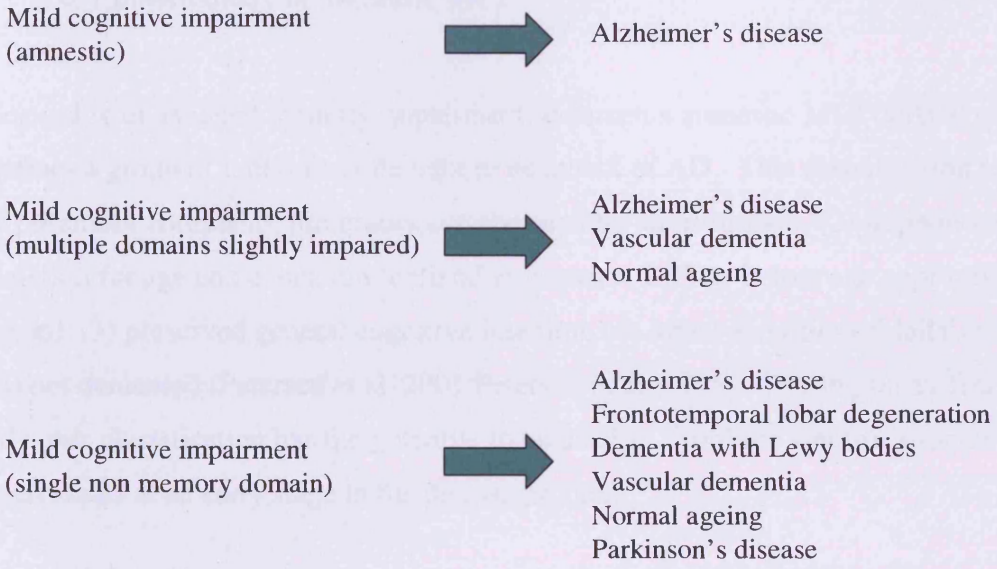


Figure 2-2 Heterogeneity of the term 'mild cognitive impairment'

from Petersen et al 2001 (Petersen et al. 2001)

As discussed, many different terms have been used to describe either what have been perceived as ageing phenomena or pre-dementia states. Such descriptions are useful in

raising the profile of groups potentially amenable to disease modifying therapies, and in providing estimates of prevalence and incidence in the population of cognitive impairment and pre-dementia states. However, with so many classifications in use there are a number of drawbacks. First, projections for conversion from a pre-dementia state to dementia often differ depending on the classification used. Second, these different patterns of cognitive impairment may be the manifestation of several underlying diseases. It is not possible, therefore, to draw definite conclusions regarding the natural disease courses of the underlying aetiologies. Furthermore, more broadly inclusive criteria such as CIND include individuals with a more heterogeneous range of underlying disease processes than more restrictive criteria such as aMCI. Conclusions drawn from studies of these two entities are therefore not easily comparable.

Amnestic MCI describes a group of individuals with memory impairment at high risk of future progression to Alzheimer's disease. As the subject of this thesis is to examine whether individuals with symptoms of memory loss are likely to progress to a diagnosis of AD, the rest of this chapter will be restricted to aMCI.

2.4. Epidemiology of amnestic MCI

Focussing on isolated memory impairment, Petersen's amnestic MCI (aMCI) criteria defines a group of individuals thought to be at risk of AD. This classification requires: (1) Memory complaint, preferably corroborated by an informant, (2) impaired memory function for age and education (defined as scores > 1.5SDs below age appropriate mean), (3) preserved general cognitive function, (4) intact activities of daily living and (5) not demented (Petersen et al. 2001;Petersen et al. 1995). Sharing many features of AD, this classification has the potential to be used as a tool for identification of individuals at an early stage in the disease process.

Although the prevalence of aMCI has been estimated at around 3% in both clinical (DeCarli 2003) and population studies (Busse et al. 2003;Ritchie et al. 2001), conflicting data are available regarding the association with gender. Some have found aMCI to be equally common in males and females (Fisk and Rockwood 2005), whilst others have found males more likely to be affected (Ganguli et al. 2004). It is perhaps surprising that the sex ratio should differ from that found in AD where women are more

commonly affected than men. It has been suggested that this female predominance in AD may result from differences in longevity of life and disease duration or may be an artefact due to poor age adjustment in studies(Baum 2005).

The prevalence of MCI has been generally shown to increase with age. Most studies have found a lower rate of MCI in the 65-74 age range, than in those between 75-84(Panza et al. 2008)with a prevalence of 15% under the age of 75 to 30% over the age of 85(Lopez et al. 2003). Others, such as the PAQUID study have found no such relationship, although these authors felt that this resulted from age already being taken into account when choosing the cut off scores that defined MCI(Larrieu et al. 2002).

Limited literature is currently available regarding whether MCI in a younger age group may be different to MCI of later onset. In the same way that the characteristics of early AD (presentation, rate of decline, genetics) differ from later onset AD, it is possible that as a preAD stage, this may hold true for MCI as well. Interestingly Geslani et al (Geslani et al. 2005) did find a higher rate of conversion to AD in their younger MCI cohort (average age 73.07$\pm$7.72, annual conversion rate 40%) than that of the older cohort of Petersen et al (Petersen et al. 1999)(average age 80.9$\pm$1,annual conversion rate 12%). However the different referral pathway for these cohorts was thought to have acted as a confounding factor.

2.5. Progression to AD

2.5.1. Rates of progression between population and clinical studies

Clinical studies indicate that around 10-15% of individuals with aMCI progress annually to a diagnosis of AD compared to 1-2% of healthy controls (Petersen et al. 2001). The conversion rate is thought to be 80% at 6 years. In community-based studies the conversion rate has been found to be slower (5-10% per year) with a substantial proportion improving their cognitive performance over time (Palmer et al. 2002;Ritchie et al. 2001). Ritchie et al found that a diagnosis of aMCI at baseline was not a significant determinant of AD at follow up. Only 7-17% in their study retained that diagnosis one year later and only 11% in total progressed to AD over 3 years. This

suggests that the diagnosis of aMCI within the context of a population study is not necessarily a stable one.

The differences in progression to AD seen between clinical and population studies may result from a number of sources. The inherent selection bias in clinical populations may lead to more individuals in the early stages of AD being recruited. Alternatively, subtle alterations to clinical criteria may substantially change the risk of progression to AD. Fisk et al found that, depending on whether subjective memory complaints or intact activities of daily living were included in the criteria for aMCI, the rates of progression to dementia after a 5-year period changed from 38.1% to 77.8%. They found that the highest risk of progression was associated with both subjective and objective memory impairment and intact activities of daily living, and suggested that this group might be best motivated to self-refer to memory clinics (Fisk and Rockwood 2005).

In longitudinal population studies, criteria may often be retrofitted to the study cohort where the study was not originally designed to diagnose MCI by consensus criteria. This can lead to conceptual and practical difficulties as not all relevant variables to the criteria may be available or those available incompletely specified. Consensus criteria also incorporate clinical judgement and are not derived from test cut-off points, consequently, such criteria are more difficult to standardize in larger population studies than smaller clinical cohorts and so are less reliable.

The lack of stability in the diagnosis of aMCI, with some patients progressing to AD, others staying stable, and others improving, suggests heterogeneity in the underlying cause within this group. Lack of progression suggests a static cerebral insult such as a strategic infarct, with improvement in performance perhaps pointing to psychosocial factors present on the day of testing but not present subsequently, e.g. anxiety or depression. An alternative explanation is that individuals originally diagnosed with aMCI would progress to AD if given sufficient follow-up time(Morris et al. 2001). At least three studies of AD have found that one in seven cases show only slow progression (Bowler et al. 1998;Holmes and Lovestone 2003;Perrault et al. 2002).

2.5.2. Markers and rates of progression of aMCI to AD

Biomarkers such as increased CSF Tau (Sunderland et al. 1999), genetic markers such as ApoE genotype (Petersen et al. 1995), ratings of memory complaints (Jonker et al. 2000), and neuroimaging changes such as measures of cerebral atrophy and altered cerebral glucose metabolism have been proposed to be able to predict which individuals will convert from aMCI to AD. Neuropsychological markers have also been investigated. Individuals with evidence of involvement of more than one cognitive domain have been found to be more likely to progress to a diagnosis of AD (Bozoki et al. 2001). Neuropsychological predictors of decline as well as neuroimaging will be discussed in detail in the following chapters.

2.5.3. Neuropathology in aMCI

Data on neuropathology are often difficult to find, as individuals with aMCI tend to die of unrelated causes rather than due to aMCI itself. However Morris et al (Morris et al. 2001) did demonstrate that in their group of individuals classed as MCI, signs of pathology of a severity between normal elderly individuals and patients in the early stages of AD were present. Riley et al in the Nun study(Riley et al. 2005) found that NFT pathology and clinical symptoms were strongest in their memory impaired group, with the proportion of individuals with non-memory cognitive impairments declining steadily as Braak and Braak staging increased.

2.6. Limitations of aMCI and the definition of normal general cognition

2.6.1. General limitations

It has been argued by some that the aMCI criteria are overly exclusive, identifying a group of individuals of value for studies in research centres but not representative of the general population. More inclusive case definitions, such as those used to identify CIND and AACD, are thought to reflect pre-dementia states in the community, yielding higher population prevalences whilst also conferring an increased risk of dementia. Investigation of aMCI alone is insufficient to gain a complete picture of prevalence and outcome of pre-dementia states in the general population. The construct of MCI has also been criticised as difficult to operationalize. There has been no standardization of

the neuropsychogical tests used to measure cognitive impairment, nor has an agreement been reached on how best to define normal cognitive function. These inconsistencies can lead to different study outcomes and make direct comparisons between studies problematic.

2.6.2. Normal general cognition

Many different definitions of 'normal' general cognition have been used within the criteria of MCI. General Cognition has been measured using clinical rating systems such as the CDR (Morris et al. 2001), on the result of a single test such as the mini mental state examination(MMSE) (Elias et al. 2000;Folstein et al. 1975;Linn et al. 1995), or on scoring above a predetermined level on a combination of tests e.g.: from the CAMCOG (van der Flier et al. 2005)or Dementia Rating Scale(Petersen et al. 1999;Tierney et al. 2005). Choice of system has often depended upon the size of the study, the historical preferences of a centre and whether extra information from an informant is considered important. Large population studies often rely on short, easy to administer questionnaires, or tests, which can be administered over the telephone, by a variety of health professionals. Some groups have avoided making a judgment on general cognition based on baseline performance, instead using the subsequent development of dementia during the course of the first year of their study, as evidence of baseline cognitive impairment (Grober et al. 2000).

To date there is no standard accepted approach for how to determine normal general cognition. The International Working Group on MCI (Winblad et al. 2004) has advised a combination of clinical judgment and neuropsychological tests, as well as other investigations. At this consensus meeting it was agreed that both cognitive and functional abilities need to be considered in the evaluation of cognitive impairment. In addition it was felt that within a clinical setting although the degree of impairment could be assessed neuropsychologically, fulfillment of MCI criteria should ultimately be determined through clinical judgment using this information and other investigations. They suggested that individual slopes of decline in both functional and cognitive performance might be better measures than deficits assessed according to age-specific norms on a single occasion.

2.7. Preclinical dementia – evidence for a pre MCI stage

With a high rate of progression to AD, the aMCI criteria identify an important group of patients for targeted treatments aimed at secondary prevention of dementia. However, even at a stage where only memory is impaired, significant neuronal destruction is already demonstrable in the brain. Disease modifying therapeutic intervention at this stage may not achieve as good an effect as it would if given at an even earlier stage. The challenge is to identify individuals for treatment prior to demonstrable cognitive deficit at a pre aMCI stage, when they may only have symptoms of memory impairment.

There is evidence that the changes associated with development of AD can even be detected prior to the appearance of cognitive deficits. Some studies have shown that subtle deficits in verbal and visual recall demonstrable on neuropsychological assessment can be predictive of future cognitive impairment (Elias et al. 2000;Fox et al. 1998). Similarly, magnetic resonance imaging (MRI) studies of presymptomatic familial Alzheimer's disease (FAD) subjects and patients developing sporadic Alzheimer's disease show a preclinical phase of neurodegeneration where rates of cerebral atrophy increase at a stage prior to fulfilment of criteria for MCI (Rusinek et al. 2003;Scahill et al. 2002). These early deficits are commonly accompanied by complaints of memory impairment which may precede demonstration of a cognitive deficit. It is unclear how long this pre-cognitive impairment prodromal phase lasts, although neuropathologic changes consistent with AD have been found to be present up to 20 years prior to the age of onset of AD (Hyman 1992) in patients with Down's Syndrome.

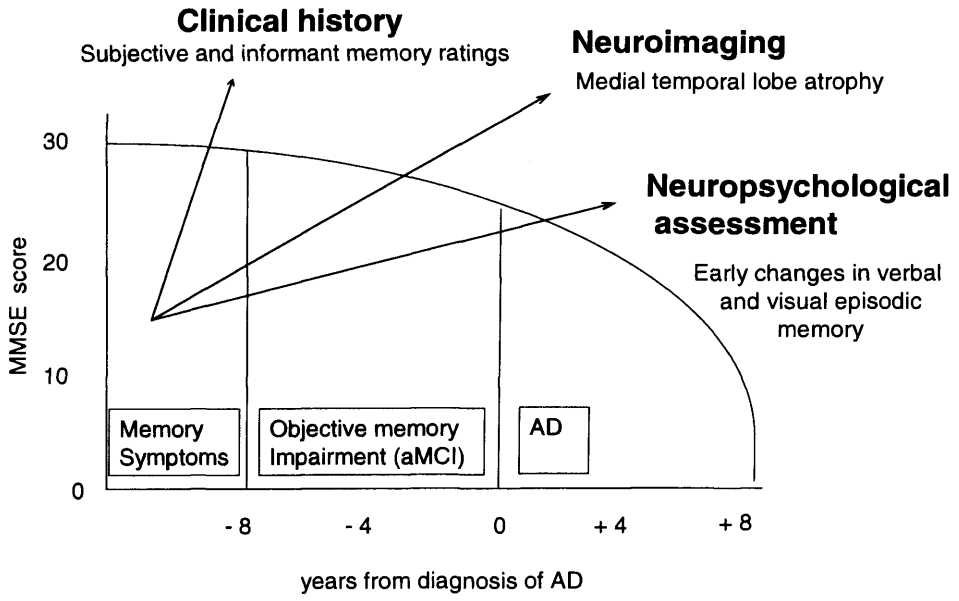


Figure 2-3 Commonly used methods employed to detect 'pre amnestic MCI'

Although the majority of individuals with aMCI are thought to progress to AD, a proportion remain stable in their cognitive impairment or improve, reflecting heterogeneity in the underlying disease process. Consequently, assigning a diagnosis of aMCI is often complex and the result of an interplay between subjective complaints, arbitrary cut-offs on neuropsychological performance, informant impression and clinician's assessment. It is only by relying on these methods that the correct 'Pre AD' subgroup can be identified from among what are often complex and multiple pathologies.

In the following chapters each of these diagnostic tools is examined to assess their relative abilities in differentiating this heterogeneous group and in detecting the subtle changes associated with pre-clinical aMCI.

3. Symptoms of memory impairment

3.1. Symptoms of memory loss as a marker for preclinical disease in AD

Symptoms of memory loss may be the first indication of the presence of an underlying neurodegenerative disease, most commonly AD. It is often the presence of these

symptoms that causes an individual to seek help from his or her general practitioner or memory clinic. Their importance is recognised in the criteria for the pre-AD state aMCI, where symptoms of memory impairment are an essential component.
Evidence for early memory impairment in AD comes from several sources. In studies of familial Alzheimer's disease (FAD), subjects at risk who subsequently developed FAD commonly had symptoms of episodic memory problems (Fox et al. 1998). In this series the subject, spouse or close family member typically noticed these problems six months prior to cognitive deficits being noted on psychometric testing. Similarly in sporadic AD, memory symptoms have been found to be present up to 2 years prior to decreased scores in the MMSE (Laakso et al. 1995). Murphy et al found in some cases that the duration was greater than 6 years (Murphy et al. 1993). These studies suggest that symptoms of memory loss may represent subtle changes in functioning as a consequence of very early neurodegenerative disease.

3.2. Memory complaints in the normal population

3.2.1. The prevalence of memory complaints in the general population

Although potentially a sensitive marker for AD, symptoms of memory loss are very common, and some 22 to 56% of the population report that they feel that their memory is not as good as it should be. Prevalence rates depend on the age and baseline cognitive status of the sample population. Studies including younger individuals show a lower prevalence whilst those canvassing institutionalized subjects tend to be higher (Jonker et al. 2000). The number and type of memory complaints reported also depend on whether and how information is volunteered or solicited. Some studies have used validated questionnaires assessing type as well as severity of memory complaints, whilst others have asked just one question such as 'Do you find that you have trouble with your memory?' or 'Is your memory getting worse?'.

3.2.2. Factors affecting perception of worsening memory in normal ageing

Independent of underlying disease, the perception that memory function is worsening varies within the normal ageing population. Certain factors such as depression, anxiety,

increasing age and lower educational levels are all associated with an increased likelihood of symptoms of memory loss (Jonker et al. 2000). Personality traits such as conscientiousness and neuroticism, and cultural factors such as perception of how memory should change over time, all colour the report of memory complaints (Lane and Zelinski 2003;Zelinski and Gilewski 2004).

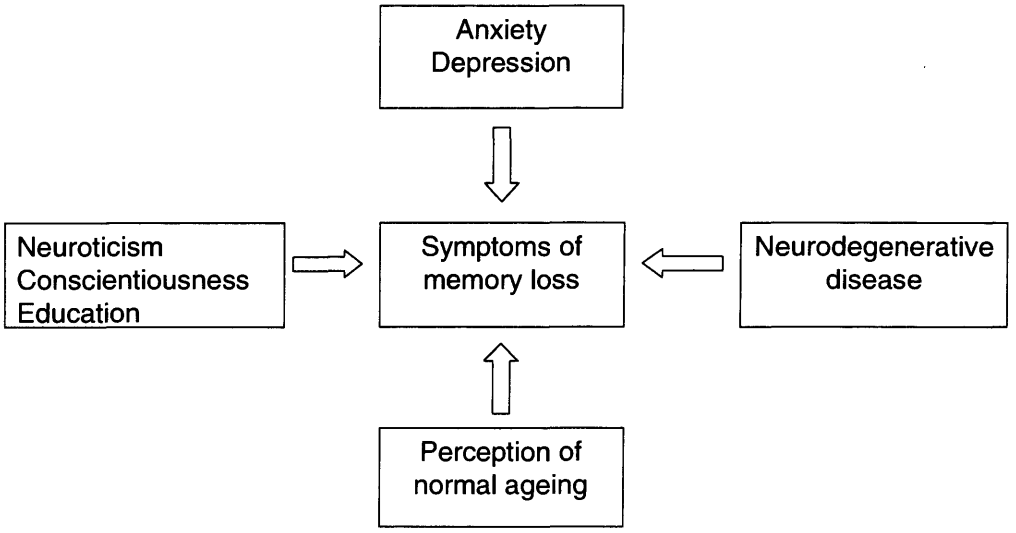


Figure 3-1 Different factors contributing to symptoms of memory loss

3.3. The prediction of present and future cognitive impairment using symptoms of memory loss. Evidence from population and clinical studies

3.3.1. Cross-sectional studies

Although symptoms of memory loss can be caused by many environmental and social factors, in some individuals they will be linked to underlying neurodegenerative disease. This relationship between symptoms of memory loss and cognitive impairment has been explored in cross-sectional community-based cohorts and has been found to be present in a number of studies. Some have suggested this to be dependent on the presence of depressive symptoms or related to cultural background (Jorm et al. 2004;Lam et al.

2005); others have proposed that memory symptoms only represent depressive symptomatology (McGlone et al. 1990). This has been more commonly reported in clinical than community based cohorts (see Jonker et al for review)(Jonker et al. 2000). One weakness in the data from cross-sectional studies is their use of arbitrary cut-offs on a single psychometric assessment to define cognitive impairment. High functioning individuals may attain memory test scores that fall within normal limits, but reflect a large drop in performance based on premorbid estimates. In addition, cognitive impairment may be found on a single neuropsychological assessment where poor performance is actually related to education, age, cultural background or illness. Longitudinal studies have the advantage of allowing comparison of performance over several assessments, providing a measure of change in cognitive ability with time. Where cross-sectional studies relate symptoms of memory loss to present cognitive impairment, longitudinal studies can assess whether symptoms of memory loss can predict future cognitive decline.

3.3.2. Longitudinal studies

Many (Johansson et al. 1997;Tobiansky et al. 1995) but not all (Jorm et al. 1997) longitudinal population studies have found subjective memory complaints to be associated with an increased risk of cognitive decline or dementia. For several groups, however, this relationship depended on the presence of a negative affect (Jorm et al. 2001;Tierney et al. 1996) or whether baseline cognitive impairment was present (Schofield et al. 1997) or absent (Geerlings et al. 1999). Different outcomes may result from variation in the length of time that a cohort is followed. However, cognitive decline has been noted after as little as one year and dementia after two. Clinical longitudinal studies have not been as widely reported. O'Brien et al found that in his group of referred individuals with symptoms of memory loss 10% had converted to a diagnosis of dementia after 3 years, whilst the remainder showed a modest decline in cognitive performance (O'Brien JT 1992). A more recent study following individuals with normal baseline cognition noted that self referral or referral by family or a physician to memory disorder clinics resulted in a conversion rate to dementia of at least 9% a year (Edwards et al. 2004). This is compared to a conversion rate to MCI or AD of 1-2% per year in cognitively normal community dwelling elders (Petersen et al.

1999). Symptoms of memory loss therefore seem to be more useful in predicting future cognitive decline than reflecting current cognitive functioning.

3.3.3. Differences between clinical and population studies

The relationship between symptoms of memory loss and future cognitive decline may vary depending on the source of study cohort. Population studies, although large and representative of a wider population, are necessarily restricted by numbers in the extent of clinical, neuropsychometric and neuroimaging assessments that can be conducted. Often, brief cognitive screening batteries are used that have a limited ability to detect subtle cognitive impairment, particularly in high-functioning individuals. Baseline cognitive functioning may be estimated using only functional guides such as the Clinical Dementia Rating (CDR) leading to a low recognition rate (Lam et al. 2005). Comparison between studies can be difficult due to differing inclusion criteria, methods of eliciting and quantifying memory complaints and neuropsychometric tests employed. In addition, the importance of subjective memory complaints may depend on whether individuals demonstrate help-seeking behavior for their perceived deficits. Most population studies canvass subjects for memory problems whilst clinical studies rely on self, family or physician referrals. Jorm et al found that those individuals who sought help for their memory problems had poorer performance on cognitive tests, were more likely to be depressed or anxious and in poorer physical health (Jorm et al. 2004). Clinical studies tend to evaluate a smaller number of individuals from a younger age range who are highly selected as a consequence of both the referral process and study inclusion criteria. These are drawbacks when applying findings from these studies to the general population.

3.4. Informant reports in early AD

Assessment of subjective memory complaints can be problematic as they are often colored by personality traits, social and environmental factors. Furthermore, without accurate knowledge of the premorbid state it is difficult to gauge whether the severity of symptoms has changed. An alternative to using subjective memory complaints in an assessment is to use the observations of an informant (i.e., spouse or relative). An informant's impression of their spouse's or relative's memory is likely to be more

objective and less influenced by patient anxiety or depression and several studies have emphasized their importance.

3.4.1. Relationship of informant reports to cognitive impairment

Informant ratings, similar to subjective memory ratings, provide a measure of everyday functioning, are culturally fair and can provide a direct measure of change, which may not be available from a single neuropsychological assessment. Informant ratings have for the most part been reported to correlate well with clinical state and performance on memory tests (Jorm 1997;Kemp et al. 2002;McGlone et al. 1990;Ready et al. 2004). Some studies have even found informant ratings to be more sensitive and specific for cognitive impairment than brief cognitive tests alone (Jorm 1997). By combining informant ratings with brief cognitive tests other groups have found that diagnostic accuracy can be improved (Mackinnon et al. 2003;Mackinnon and Mulligan 1998;Tierney et al. 2003), although this has not been shown in all studies (Knafelc et al. 2003). Similarly, longitudinal studies have shown that informant ratings contribute significantly to the prediction of AD in primary care cohorts (Tierney et al. 1996) and studies based on populations (Carr et al. 2000).

3.4.2. Reliability of informant reports

Although informant reports are generally regarded as useful, their reliability can also be affected by a number of factors. Those informants living with the subject tend to provide more valid reports about the subject's memory ability than those who do not(Ready et al. 2004). This may be due to relationship status, as most live-in informants are spouses. Educational history, quality of relationship, informant depression and frequency of seeing the subject have all been found to affect the reliability of a rating. Older, less educated informants not living with the subject and seeing them only infrequently are considered to be less reliable (Cacchione et al. 2003). Informant reports may not agree with the results of cognitive tests where informants view loss of memory as a normal part of ageing or are unwilling to accept that someone on whom they depend is decompensating. Watson et al found that as a subject became increasingly impaired the informant report became less reliable (Watson LC et al.

2004). The opposite was found by Kemp et al who associated less reliable informant reports with milder degrees of impairment (Kemp et al. 2002).

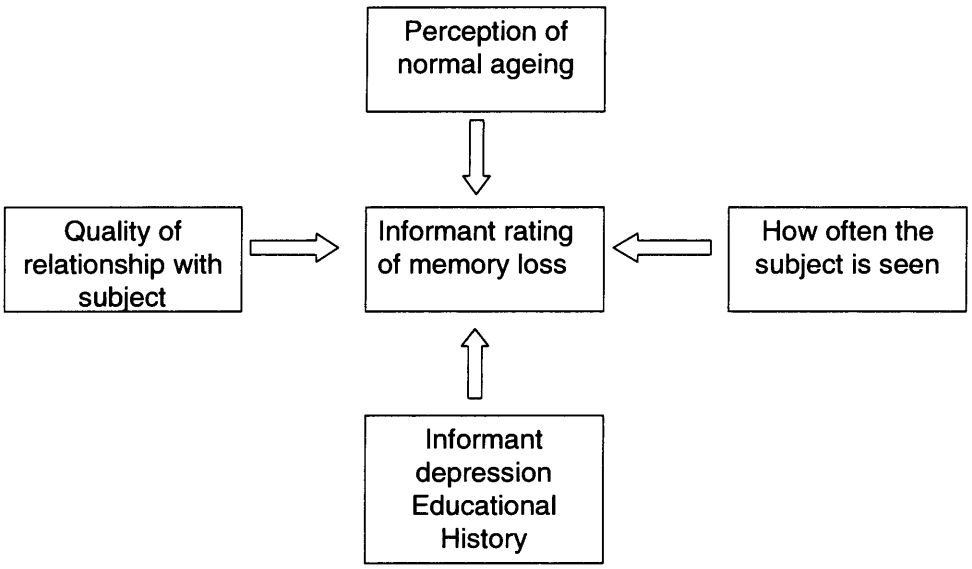


Figure 3-2 Factors affecting the reliability of informant reports

3.4.3. Cognitive impairment without symptoms of cognitive impairment

To fulfil the Petersen criteria for aMCI, an individual must have memory complaints in addition to memory impairment. One criticism of these requirements is that when applied to the general population they may at best misrepresent the true number of individuals with impaired cognitive functioning, and at worst risk basing MCI research on an exclusive and potentially biased sample. The level of insight an individual has into their memory performance is thought to vary with disease progression. At the earliest stages Rabin et al suggest that individuals can be more aware of their cognitive impairments than their informants. These subjects with either MCI or cognitive complaints alone identified areas of cognitive weakness that were also identified by their informants but to a lesser degree. Similarly Kalbe et al (2004) found that subjects with MCI reported significantly more cognitive impairment in comparison to their informants, whilst AD patients complained of less. Ott et al has also described limited insight into cognitive difficulties in established AD. Although there seems to be a

continuum of insight, with those with milder impairments displaying most symptoms, there is concern that in the community there may be a group of individuals with cognitive impairment but no symptoms, equally at risk of a dementing process. Purser et al (2006) found that non symptomatic MCI subjects comprised 14% of their overall community cohort whilst those fitting the Petersen criteria comprised only 8.9%. Importantly clinical outcome measured by activities of daily living at 10 years was similar between these two groups.

Symptoms of memory impairment in addition to objective cognitive impairment are accepted as representing a high risk for progression to AD. In situations where an individual makes contact with medical services as a result of a memory complaint, the Petersen criteria are helpful in defining that individual's risk of disease progression. Nevertheless, it is important to recognise that whilst useful in a clinical setting these criteria should be applied carefully to the population as a whole.

3.5. Use of memory aids in AD

As well as documenting subjective and informant histories, note can be made of whether an individual uses memory aids to overcome their symptoms. Lane et al (Lane and Zelinski 2003) found in their longitudinal study that subjects with smaller declines in memory function over time were more likely to use memory strategies and aids. They suggested that the use of memory aids might lead to better day-to-day functioning despite the presence of subtle memory difficulties, and thereby render their cognitive deficits less noticeable to their informants. In this way the use of different memory aids such as calendars, diaries and notepads reflects insight into memory difficulties with an intentional utilization of compensatory techniques. With progression of memory impairment as in AD, this usage may decrease due to difficulty in using the aids and limited insight into memory failings as a result of the disease process (Ott et al. 1996).

3.6. The relationship of subjective and informant ratings of memory loss to other disease markers and post mortem studies

As well as relating subjective and informant memory ratings to clinical stage and cognitive performance, some studies have sought to assess how memory ratings correlate with other markers of early AD. Small hippocampi as identified by quantitative MRI are among the first changes seen on neuroimaging in AD compared to images obtained from normally ageing controls (Jack, Jr. et al. 1992) (see chapter 5). Farias et al found a relationship between hippocampal size and informant ratings although this correlation was explained by the effects of age on hippocampal size (Farias et al. 2004). Jorm et al related symptoms of memory loss in a group of non-demented men to the presence of neurodegenerative disease in the brain at post mortem. Adjusting for age at death and the interval between clinical examination and death, memory complaints were found to predict both AD and any dementia-related neuropathology (Jorm et al. 2004).

3.7. Using symptoms of memory loss to identify early AD

One of the drawbacks of many memory studies that have been conducted to date is that subjects often have a wide range of general health problems, including cerebrovascular disease (CVD), psychiatric history or malignancy. Where this is the case, any symptoms of memory impairment unrelated to psychosocial factors could potentially have several aetiologies, for example, vascular disease and Alzheimer's disease. In our study we limited our investigation to the relationship between symptoms of memory impairment and the development of Alzheimer's disease and we have included only those individuals with mild memory impairment (normal general cognition) who have been screened for the presence of strategic infarcts or widespread vascular disease as well as reversible causes of memory impairment (e.g., depression or metabolic disorders).

3.8. Summary and conclusions of symptoms memory loss

Symptoms of memory loss are an early indication of the presence of AD, apparent even before cognitive changes are demonstrable on psychometric testing. Although sensitive, they are not specific for this disease process, as a wide range of social and psychological factors can affect an individual's perception of their memory. Different pathological processes such as vascular, degenerative and metabolic diseases can also manifest with memory symptoms. In terms of predicting cognitive decline, symptoms of memory impairment have been shown in both population and clinical studies to be associated with future cognitive impairment and dementia. These symptoms may be particularly important in high-functioning individuals where neuropsychological tests are not sensitive enough to detect subtle deficits in cognitive functioning(Archer et al. 2005). Informant ratings of memory loss may have advantages over subjective memory ratings as they are free from the depression and anxiety that may colour subjective complaints. They have been found to correlate well with measures of cognitive impairment in both cross sectional and longitudinal studies.

Aside from their role in screening for incipient dementia, subjective symptoms of memory loss do provide a measure of perceived everyday memory problems, as well as providing information on an individual level on insight and awareness of problems. Objective memory tests may not necessarily test everyday skills such as managing a household, or carrying out chores, and therefore may not be predictive of everyday performance. Symptoms of memory loss in combination with tests of memory provide a fuller picture of an individual's daily functioning and memory difficulties.

In conclusion, symptoms of memory loss and informant ratings may be useful in identifying individuals at a 'Pre aMCI' stage, which would be most amenable to treatment with disease modifying therapies. Although in themselves sensitive gauges, they would be best used in combination with other modalities such as neuropsychological tests and neuroimaging to increase the specificity of a diagnosis of pre clinical AD. In the following chapters we assess the abilities of neuropsychological tests and neuroimaging to detect early neurodegenerative disease.

4. Neuropsychology

4.1. Introduction

Cognitive impairment in an individual is assessed using neuropsychological tests, with performance evaluated through comparison to a set of 'normative' values. These values are derived through testing a large number of individuals from a 'healthy control' sample. By establishing which tests indicate impairment in an individual and therefore which cognitive domains are involved, a profile of cognitive impairment can be defined. Certain neurodegenerative diseases like AD have characteristic cognitive profiles.

4.2. Progression of neuropsychological abnormalities with disease state

The pattern of decline associated with early Alzheimer's disease characteristically begins with deficits in verbal then visual memory before progressing to involve the cognitive domains of naming, language, visuospatial skills and executive function (Lambon Ralph et al. 2003).

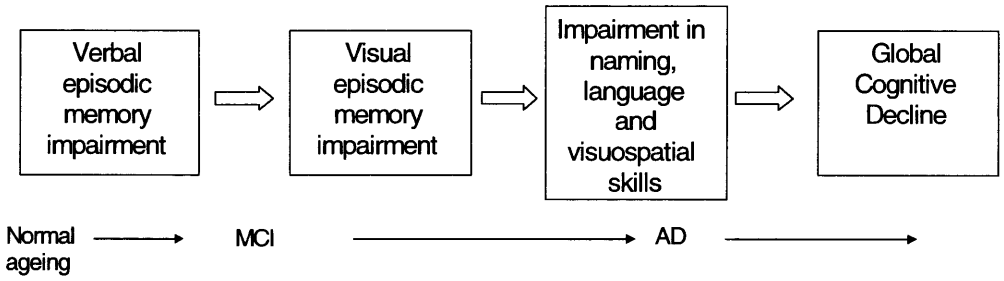


Figure 4-1 Progression of cognitive deficits from amnestic MCI to AD

4.3. Neuropsychological measurements as predictors of cognitive decline

Early neurodegenerative disease can be detected with neuropsychological assessment. Amnestic mild cognitive impairment discussed in the previous chapter describes individuals found to have isolated memory deficits at assessment. However, studies of normally ageing individuals who subsequently become cognitively impaired and individuals in the early stages of FAD suggest that whilst an individual's performance may still be within the normal range, subtle changes in functioning are demonstrable at a group level in those who progress to cognitive impairment (Fox et al. 1998;Linn et al. 1995). These cognitive changes have been assessed by both cross-sectional and longitudinal studies.

4.4. Cross-sectional studies

To detect subtle presymptomatic changes in cognitive functioning, cross-sectional studies of individuals thought to be at increased risk of development of AD (e.g., by virtue of a first degree relative with AD, or the presence of an ApoE4 allele) have been undertaken where neuropsychological performance in this 'at-risk' group is compared to a group of matched controls. Poor performance on any test by the at-risk group compared to the normal group is considered to reflect cognitive changes characterising the earliest stages of AD. One of the major drawbacks of such a study design has been that, except for known genetic mutations such as APP, Presenilin 1 or Presenilin 2, other risk factors do not confer a 100% risk of development of AD. As a consequence any deficits observed in such a cohort may well be related to the presence of various risk factor as opposed to an early change associated with the development of AD. In addition these studies do not indicate whether impairment is static or progressive. For this reason the majority of information surrounding the earliest changes in cognitive functioning detectable in AD come from longitudinal studies.

4.5. Longitudinal studies

In these studies a large cohort of study subjects are recruited and a battery of neuropsychological tests are administered at entry to the study. Future cognitive

performance is then compared to these baseline results. After an appropriate period of follow up the study participants are reassessed and the baseline cognitive performances of those who progressed to a diagnosis of aMCI or AD are compared to those in the study cohort remaining healthy. Differences in cognitive profiles are assumed to represent the early changes in cognition found in aMCI or AD.

Longitudinal studies have suggested that the earliest identifiable differences at a group level are changes in both verbal and visual episodic memory (Flicker et al. 1991;Linn et al. 1995);(Amieva et al. 2005;Kawas et al. 2003). Others have proposed the early involvement of abstract reasoning and linguistic ability (Elias et al. 2000;Jacobs et al. 1995;Snowdon et al. 1996). Most studies have found a sparing of semantic memory, including verbal fluency and naming, during the early stages of decline (Fox et al. 1998) (see Collie et al 2000 for review(Collie and Maruff 2000)). With established mild cognitive impairment other domains of cognition are recruited into the spectrum of deficits (see Figure 4-1). Table 4-1 displays a list of longitudinal studies that have followed subjects thought to be 'cognitively normal' at baseline who subsequently developed AD, thus demonstrating which cognitive tests were found to be most strongly associated with development of AD.

Table 4-1 Longitudinal studies identifying presymptomatic cognitive change

These cohorts had 'normal' cognition at baseline assessment

Study	Population	Prior to diagnosis	Best predictor
Bondi 1994	At-risk characterised by a family history of AD	1-2 yrs pre AD	Episodic memory
Masur 1994	Bronx aging study	4 yrs pre dementia	Memory, verbal fluency, executive functioning
Jacobs DM 1995	North Manhattan Ageing Project	2 yrs average	Word finding, abstract reasoning and episodic memory
Snowdon 1996	The Nun Study – autobiographies written at 22.	Up to 58 yrs prior to AD	Linguistic ability – idea density,

Tierney et al 1996	Referrals from family physician	2 years prior to AD	Episodic memory
Fox et al 1998	FAD research cohort	2-3 yrs pre symptoms, 4-6 preAD	Verbal episodic memory and measures of intellectual Quotient
Elias et al 2000	Framingham (community)	10 yrs pre AD	Episodic memory and abstract reasoning
Kawas 2003	Baltimore Longitudinal study of aging	Up to 15 yrs pre AD	Visual memory
Amieva et al 2005	PAQUID cohort (population)	9 yrs pre AD	Visual memory, verbal fluency, abstract reasoning
Galvin 2005	Community based	>6yrs pre AD	Practice Effects

4.5.1. How long prior to development of AD are neuropsychological changes detectable on neuropsychological assessment

Many longitudinal studies have sought to establish how many years prior to the onset of dementia these neuropsychometric changes are detectable. In presymptomatic familial AD subjects Fox et al found that performance on tests of verbal recognition memory and performance intellectual quotient (PIQ) was characteristically decreased, relative to controls, 2-3 years prior to onset of symptoms(Fox et al. 1998). With an often less aggressive disease course longer periods between cognitive deficit and diagnosis of AD have been described in sporadic AD. In the Framingham Study cohort, the surveillance period was 22 years. During this time 109 of 1076 initially non-demented individuals went on to develop AD. When baseline cohort scores for the AD and non AD group were compared, the AD group had lower scores on tests of learning, immediate recall, retention and abstract reasoning at baseline than those who remained cognitively normal. In this study these changes could be detected at least five years prior to diagnosis of AD, and at ten years prior to diagnosis for tests of retention and abstract reasoning (Elias et al. 2000). Subjects were followed for an even longer interval in the Nun Study. Snowdon et al found that measures of linguistic ability, assessed from autobiography passages written at the age of 22, could distinguish those who would

have histopathological evidence of AD at post mortem up to 55 years later (Snowdon et al. 1996). Similarly, Whalley et al found lower scores on a test of general psychometric intelligence at the age of 11 to be associated with a diagnosis of late onset dementia (Whalley et al. 2000). Other groups have also found early changes in cognition to be present as many as nine and fifteen yeas prior to diagnosis of AD (Amieva et al. 2005;Kawas et al. 2003). One constraint of these studies is that due to time and resources there is a limit to how extensive a neuropsychological battery of tests can be employed. The ability to pick up early cognitive changes clearly relies on the appropriate tests with high sensitivity being incorporated into the study battery. Through inclusion of certain tests and exclusion of others, investigation of some cognitive domains may be assessed in greater detail than others.

4.5.2. Rate of change of cognitive performance - marker of preclinical AD

As well as enabling retrospective analysis of baseline cognitive performance between pre clinical AD and control groups, longitudinal studies allow quantification of the rate of change of cognitive function. Amieva et al, in their population-based study, found that the rate of cognitive change varied depending on the stage of diagnosis. Throughout their study the rate of change in those who subsequently cognitively declined on the mini-mental state examination (MMSE) was faster than controls, and accelerated three years prior to diagnosis of AD (Amieva et al. 2005;Folstein et al. 1975). This suggests that the rate of change in function seen throughout the early stages of AD may not be linear, with the tempo of decline indicating the stage of the disease process.

Some longitudinal studies have succeeded in following their study cohort to post mortem, ensuring that a definitive diagnosis is reached on each individual. One such community-based study followed 80 individuals with normal baseline cognition for an average of six years prior to death. The majority had histopathological evidence of AD although 34% had histological evidence of AD without a clinical diagnosis of AD and minimal cognitive impairment (CDR=0 (Clinical Dementia Rating)) at death. When the neuropsychological performance of this group was compared to that of the controls, it was found that they had not improved on the different psychometric tests used over the time course of the study to the same extent as the control group (Galvin et al. 2005).

This suggests that lack of 'practice effects', that is, the ability to improve on a particular test over a period of time, may be an indication of cognitive decline. This has been explored further by Darby et al who assessed whether differences in practice effects from multiple assessments over one day in a group of normal controls and MCI subjects could indicate cognitive decline. Based on practice effects they were able to identify correctly 95% of subjects and 80% of those with MCI (Darby et al. 2002).

4.6. Limitations of neuropsychological assessments

4.6.1. General limitations

Although a key instrument in the assessment of cognitive impairment, neuropsychological assessments are subject to a number of general limitations. Arbitrary cut-offs based on normal performance of a population are often used to define whether an individual is impaired in a particular cognitive domain. In the ageing population accurate normative values may not be available for older age ranges. Where normative values for all ages are available they may not be representative of performance in healthy elderly individuals. Exclusion criteria for the standardization sample for older people on the Wechsler Adult Intelligence Scale-Revised (WAIS-R) and Wechsler Memory Scales-Revised (WMS) included a history of psychiatric illness, stroke and hypertension, but none of the potential risk factors for AD or the subsequent development of AD (Wechsler 1981). Arguably, where individuals with subtle cognitive deficits have been included in normative populations, the variance reported may be over-estimated, while cut-off scores for impairment may be underestimated.

It should be noted that due to the wide range of normative values for a particular test, high functioning individuals may need to undergo a greater decline in performance than individuals with lower functioning in order to fall into a predefined impaired range. Conversely, those who have always fallen within the lower ranges of the normative range may record impaired scores that only show a small deviation from their normal capabilities. Where the same neuropsychological tests are being used on a routine basis, practice effects may affect diagnostic accuracy in cross-sectional studies, if subjects have done the tests beforehand.

Other characteristics which can render neuropsychological tests insensitive to the subtle changes present in neurodegenerative disease include the wide intra- and inter-subject variability often affected by depression, anxiety, poor motivation, fatigue, language and education (For review see Collie and Maruff (Collie and Maruff 2000)). These can increase the variability in neuropsychological performance. In this way neuropsychological assessments can be subject to the same limitations as assessments of symptoms of memory loss. Where present, a particular pattern of cognitive impairment may be useful in diagnosing or predicting an underlying disease. Although many diseases may present with the same features at an early stage, serial assessments are required to differentiate a static (eg: vascular event) from a progressive cause (AD) and one neurodegenerative disease from another (e.g. Dementia with Lewy Bodies from AD).

4.6.2. Limitations specific to longitudinal studies

Although longitudinal population-based studies have provided a wealth of information on the natural course of Alzheimer's disease, they possess a number of inherent drawbacks. First, due to the resources available for studying such large cohorts, it is often not possible to carry out detailed neuropsychological assessments, either when evaluating the baseline cognition of a cohort (as discussed in chapter 3), or when assessing outcome. This has meant that in some studies baseline cognition is only classified as demented or 'not-demented', thereby covering a range of neuropsychological deficits. These studies are most likely assessing cognitive functioning in a mix of control and MCI subjects in their 'non-demented' group and may not be directly addressing the earliest changes detectable in AD (Backman et al. 2001;Chen et al. 2000;Flicker et al. 1991). A further limitation may also be that key cognitive domains such as memory are not adequately investigated. Only those studies which have assessed their cohorts and called them 'cognitively normal' are included in table 4-1. Equally, at final assessment many longitudinal studies simply classify subjects as demented or 'not demented' rather than assigning a specific diagnosis. Those who are demented will inevitably be affected by a wider range of underlying disease processes than just AD. This restricts the number of studies that have specifically sought to evaluate both early changes and progression of cognitive impairment in early AD. A further problem is the 'drop out' that inevitably occurs in

large studies carried out over long periods. Those that are persistently followed up tend to be healthier than dropouts, a phenomenon known as selective attrition.

Finally, in those studies that have found changes up to 50 years prior to diagnosis of AD it is uncertain whether these changes are themselves consistent with early AD or simply identify a group of individuals at greater risk of developing AD. Work in Down's Syndrome (see Chapter 1 'amyloid hypothesis') has suggested that the histopathological changes associated with AD are detectable at most 20-30 years prior to symptoms (Hyman 1992).

4.7. Summary and conclusions

In summary, selected and carefully validated neuropsychological tests are essential for the assessment of individuals with suspected neurodegenerative diseases. Past research has demonstrated a pattern of cognitive impairment characteristic of AD, with the earliest changes apparent in the domains of episodic memory and abstract reasoning. These changes have been shown to be apparent as many as 15 years prior to development of AD at a group level. Research has also suggested that serial assessment is important, not only to control for subjective components such as depression or anxiety, but also to allow monitoring of any progressive change in function. It is thought that this change is not linear throughout the disease process, but accelerates around 3 years prior to diagnosis with AD. Although an important assessment tool, neuropsychological measurements have some inherent weaknesses, in terms of their sensitivity, their use of arbitrary cut-offs for impairment and, where cognitive impairment is present, their lack of specificity for diagnosis. As such they are best combined with both clinical evaluation and other investigations such as neuroimaging to increase diagnostic and predictive yield. The field of neuroimaging will be examined in the next chapter.

5. Neuroimaging

5.1. Introduction to neuroimaging in neurodegenerative disease

Cerebral atrophy is the macroscopic consequence of neuronal cell loss related to amyloid plaque deposition and NFT formation in AD. This atrophy characteristically begins in the medial temporal lobe substructures of the hippocampi and entorhinal cortex, before progressing to involve the rest of the cerebral cortex. This pattern of change first seen in histopathological studies was later visualized in vivo with development of structural imaging techniques such as computerized tomography (CT) and magnetic resonance imaging (MRI). Advances in functional imaging techniques such as single photon emission computerised tomography (SPECT), positron emission tomography (PET), proton magnetic resonance spectroscopy (MRS), diffusion tensor imaging, and functional magnetic resonance imaging (fMRI) have allowed visualization of certain biological changes associated with this disease process such as change in level of neurotransmitters. The different modalities available for imaging in AD are outlined in Figure 5-1. Structural imaging with MRI forms the main focus of this study and therefore this chapter will be limited to the application of this particular technique, with an explanation of the different technical methods employed to assess cerebral atrophy and then its application to early neurodegenerative disease. PET imaging will also be discussed.

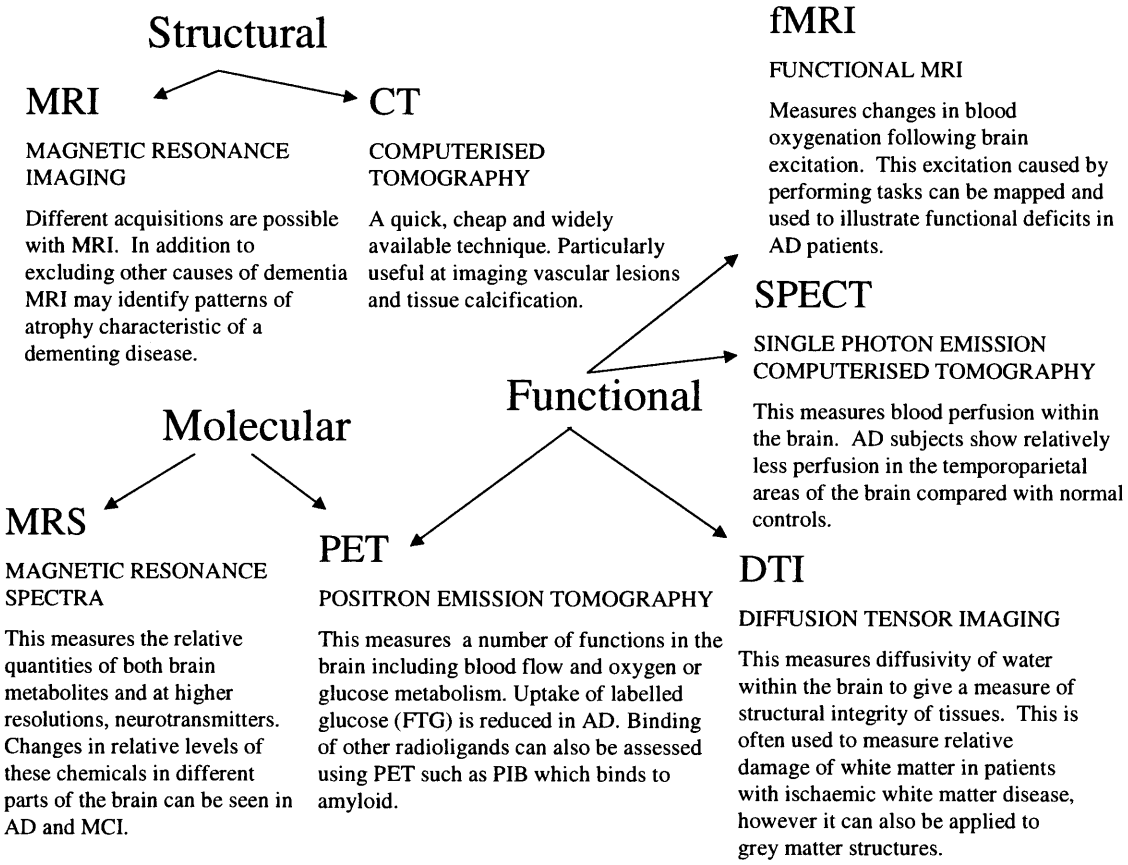


Figure 5-1 Overview of different methods of imaging used to assess the brain in AD

5.2. Structural imaging techniques

Structural imaging of the brain is an essential component of the assessment of an individual with cognitive decline. As well as allowing localisation and evaluation of cerebral atrophy, potentially treatable causes of dementia such as brain neoplasms or subdural haematomas can be excluded. Structural imaging also gives an indication of how much cognitive decline may be due to cerebrovascular disease. The application of MRI and CT to dementia is widely recognized within both European and US guidelines for investigation of possible dementia. These recommend that all patients undergo either MRI or CT (Knopman et al. 2001).

5.2.1. Computerized tomography

Computerized tomography (CT) uses X-rays to create an image that reflects absolute tissue density. In these images brain tissue appears grey and cerebrospinal fluid (CSF) black. As well as being inexpensive and widely available, the short acquisition times required by CT may be advantageous when scanning patients that have difficulty keeping still. Computerized tomography can be used to visually assess the extent and location of any small vessel disease and cerebral atrophy present. Certain CT measures such as medial temporal lobe thickness have been used to distinguish AD subjects from controls (Jobst et al. 1992). Some of these CT measurements have been extensively validated and, much like visual ratings, are quick and easy to apply in a clinical setting with relatively little training. A relatively high dose of radiation, however, is required to acquire an image and the image quality is inferior to MRI. CT scanning technology has become increasingly sophisticated in recent years but MRI is still considered the modality of choice for imaging cerebral atrophy.

5.2.2. Magnetic resonance imaging

Magnetic resonance imaging (MRI) uses radiowaves and magnetic fields to create images. In practice, this is achieved by placing an individual within a magnetic field and using a transmitter to deliver a radiofrequency (RF) pulse. Hydrogen atom nuclei in the patient absorb this energy and re-emit it when the transmitter is turned off. These emitted radiowaves are received and used for reconstruction of the image.

The strength of the field produced by the majority of MRI scanners varies between 0.15-3 Tesla (T). A field strength of 1T is 20, 000 times greater than the earth's magnetic field. Hydrogen nuclei inside the body become aligned with the magnetic field depending on its strength. As well as spinning on their own axis, the nuclei experience an additional spin called precession induced by the external magnetic field.

If a radio frequency pulse (RF) (excitation pulse) is transmitted at the precessional frequency of the hydrogen nuclei, the nuclei absorb energy, move to a higher energy level and precess in phase. When the radio frequency pulse is switched off, the protons subsequently realign with the magnetic field and emit the energy absorbed from the RF pulse shifting from a high to a low-energy state. The emitted energy signals are then converted into images.

The release of this energy takes place over a short period of time according to two constants known as T1 and T2. The T1 and T2 properties of tissues differ according to their composition (e.g., the hydrogen atoms in fat molecules absorb and emit energy much more efficiently than those in water) and can be used to differentiate one structure from another. Altering the MRI acquisition parameters so that an image is T1-weighted causes the nerve connections of white matter to appear white, while cerebrospinal fluid appears dark. This contrast is reversed using T2-weighted imaging. Extrinsic contrast parameters include the repetition time (TR) (time from application of one RF pulse to the next) and the echo time (TE) (time between a RF excitation pulse and the collection of a signal). Altering these acquisition parameters also affects the image appearance as well as scan time and quality.

In this study we have used volumetric T1 weighted scans to acquire data in three dimensions. They usually consist of around one million three-dimensional voxels[1] (each around $1mm^3$) in an adult brain. These scans have high anatomical resolution and are thus well suited to quantification of cerebral atrophy. Whole brain proton density and T2 weighted images have been used to measure white matter hyper intensities associated with cerebrovascular disease.

5.2.3. Artefacts and scan quality

Different combinations of the parameters outlined above will result in images highlighting particular tissue types. However, the quality of the scan can also be affected by a number of other factors independent of these acquisition parameters. Movement artefacts from a change of position (e.g., head movement during scanning) or involuntary physiological movement (e.g., pulsation of vessels) can result in blurring or smearing of an image. Implants of ferrous materials can affect the local magnetic field and can distort or even blackout a large surrounding area of the image. 'Aliasing' occurs when the surrounding field of view (FOV) or head coverage is too small. Signals picked up from tissues outside the FOV are falsely allocated to pixels within the matrix. This results in part of the image being shifted to the opposite side from its true anatomy. Image intensity inhomogeneity or bias is the slowly changing and smooth

[1] A voxel is the unit of volume corresponding to the smallest element depicted in a three-dimensional image

spatial variation in signal intensity that can occur within the scan. All these artefacts affect the ability to compare images over a period of time.

MRI has been established as a safe non-invasive and high resolution means of brain imaging and is increasingly available in clinical practice. MRI avoids radiation but scanners are not yet sufficiently available. In addition, the powerful MRI field used makes this unsuitable as an investigation for those patients with pacemakers or some metal implants.

5.3. Techniques used with MRI to detect neurodegenerative disease

5.3.1. Cross-sectional imaging techniques

5.3.1.1. Visual assessment

As with CT, the most common form of analysis for MRI is simple visual inspection. By identifying certain patterns of atrophy the investigator can often distinguish different neurodegenerative diseases, one from another. AD is characterized by bilateral small hippocampi in the earlier stages followed by general cerebral atrophy. The patterns of cerebral atrophy seen in different disease processes, however, can often overlap, and the wide inter-individual variability seen in brain morphology may mean that subtle changes related to early neurodegenerative disease may be difficult to distinguish from normal ageing. This has led to the development of methods of quantitative MRI analysis, more sensitive to subtle changes in cerebral structure. Some of these methods are outlined below.

5.3.1.2. Measures of brain volume

Visual inspection allows a qualitative assessment of cerebral atrophy related to neurodegenerative disease. An objective measure of the amount of cerebral atrophy present can be attained using computer-aided techniques such as whole brain segmentation. This technique requires a trained user on a computer workstation to outline cerebral structures in an automated or semi-automated fashion (Freeborough et

al. 1996;Freeborough et al. 1997;Smith et al. 2001). This measurement can then be adjusted for pre-morbid head size by correcting for total intracranial volume (TIV) (Whitwell et al. 2001) (see Figure 5-2).

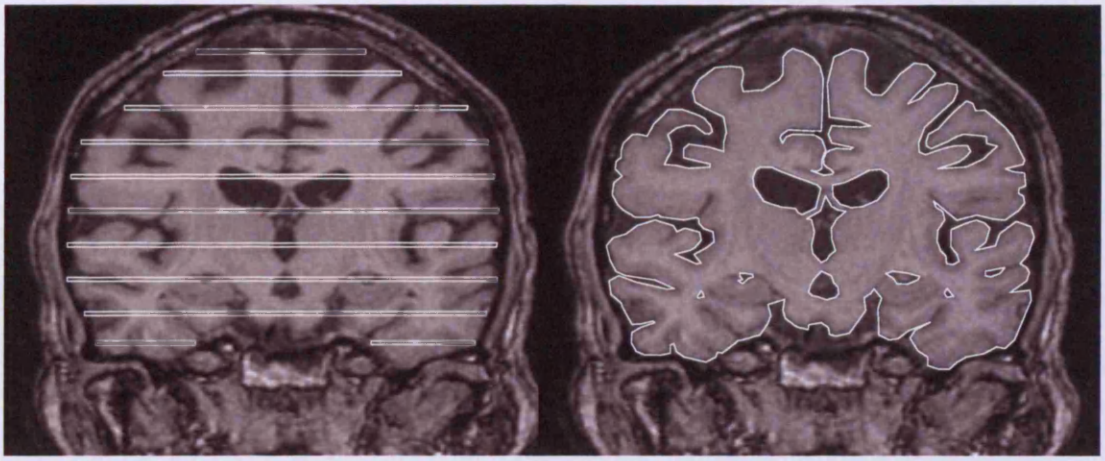


Figure 5-2 Trans intracranial volume and whole brain segmentation

Whole brain measurement is often performed on every "slice" of an MR scan. This gives an accurate estimate of brain volume, which is highly reproducible between raters (less than 2% error between raters and less than 1% within raters). TIV is often measured at regular intervals of the scan, for example, every 10 slices. This gives an estimate of premorbid brain size / head size which can be used to correct other volumetric measures, removing inter-individual variability in head size such as those due to sex differences. TIV is also highly reproducible between raters (less than 1% error within raters).

Whole brain volume analysis gives a measure of general brain atrophy but no indication of how one region has changed compared to another. As different dementias are characterized by differing patterns of atrophy, this measure is not specific enough to be diagnostically useful.

5.3.1.3. Regional measures of cerebral atrophy

Smaller brain structures or regions of interest (ROI) can also be outlined and measured to allow quantification of patterns of regional atrophy. Figure 5-3 below demonstrates the segmentation of the hippocampus, amygdala and entorhinal cortex.

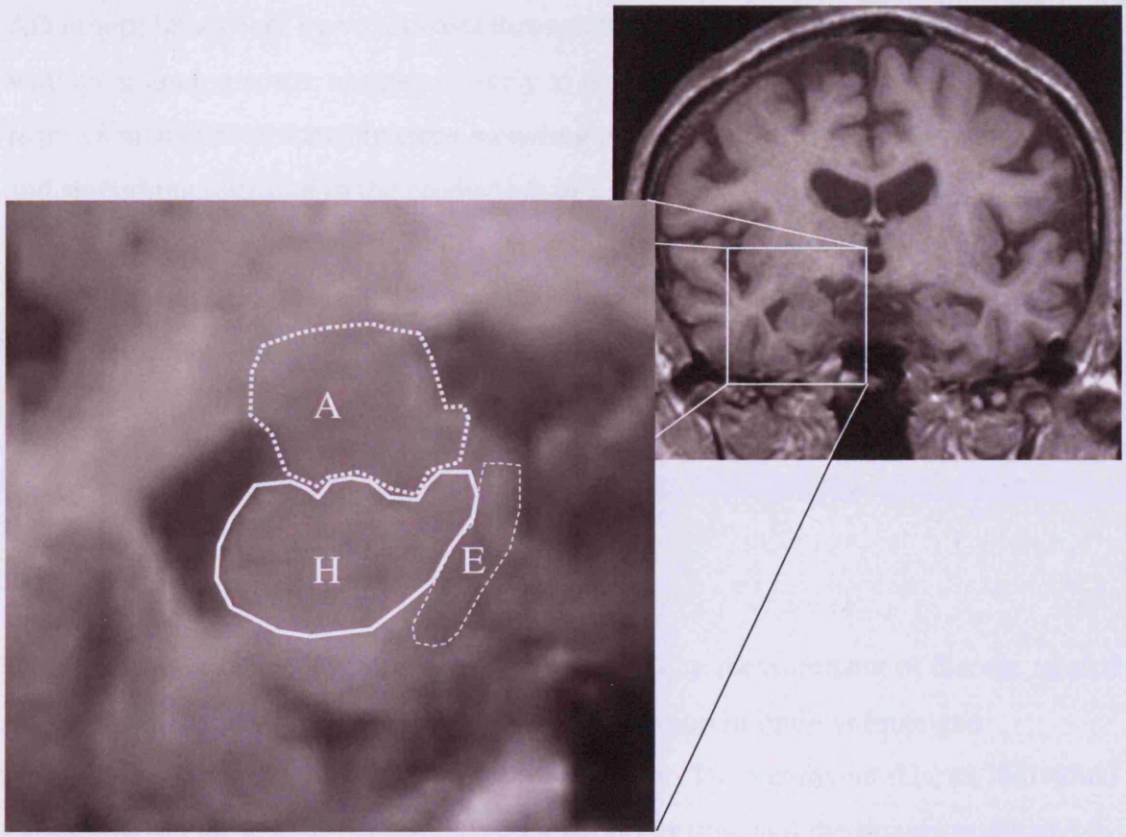


Figure 5-3: Hippocampal (H), amygdala (A) and entorhinal cortex (E) segmentation

These segmentations are usually performed on every "slice" where the structure is present, in an automated or semi-automated fashion (using pre-set intensity thresholds determined by whole brain intensity). These areas are known to be affected early in the disease over and above whole brain atrophy; however, the error in their measurement is relatively high (approximately 5% of the structure volume between raters and under 5% between raters.)

Several of these structures can also be measured (semi) automatically, (for example, the hippocampus and amygdala (Chupin et al. 2007;Fischl et al. 2002;Heckemann et al. 2006). Use of these methods can decrease the amount of time taken to outline these structures whilst maintaining reproducibility of measurements. Despite this, many techniques do require some manual intervention and few have been widely validated.

5.3.1.4. Other techniques

Other methods used in evaluating whole brain and regional atrophy include voxel-based morphometry and surface based techniques. Voxel-based morphometry (VBM) is a method used to analyse large numbers of scans on a group level (e.g. control group or AD group) on a voxel by voxel basis throughout the image. This allows analysis without assuming where atrophy is likely to be situated within the brain. Such analysis requires many pre-processing steps including normalization, segmentation, modulation and smoothing resulting in the production of tissue density maps for each group. For a detailed description of these methods see Ashburner et al (Ashburner and Friston 2000). Surface based techniques allow comparisons within and between subject groups on whole brain (cortical mapping) or smaller structures. Both these methods require many pre-processing steps. For a review see Thompson et al (Thompson et al. 2004).

5.3.2. Longitudinal techniques

One limitation to the use of cross-sectional imaging in measurement of disease related atrophy is the large degree of inter-individual variation in brain volume and substructures found within the 'normal' population. To circumvent this, an individual can be imaged on several occasions over a period of time and the images compared to each other. In this way an individual can act as his/her own control. Quantification of change between the images acquired over a certain time period allows a rate of cerebral atrophy to be calculated, and, based on this, more accurate differentiation made between normal and pathological processes. Table 5-1 shows the rates of whole brain atrophy found in healthy controls and AD subjects.

Table 5-1 Whole brain rates of atrophy in control and AD subjects over one year

Author and year of publication	Mean age (y)	Mean % rate of atrophy/y (standard deviation)
Fox and Freeborough 1997 (Fox and Freeborough 1997)	54	*C 0.24 (0.32) AD 2.78 (0.92)
Fox et al 2000 (Fox et al. 2000)	65	C 0.41 (0.47) AD 2.37 (1.11)
O'Brien et al 2001(O'Brien et al. 2001)	75	C 0.5 (0.7) AD 2.0 (0.9)
Wang et al 2002(Wang et al. 2002)	70	C 0.4 (0.5) AD 2.4 (1.2)
Schott et al 2005(Schott et al. 2005)	70	AD 2.2 (1.2)

*** Control**

5.3.2.1. Registration

To improve the visual assessment and quantification of change using serial images, scans can be co-registered (spatially matched) through a variety of techniques to differing levels of complexity. The registration process removes the effect of both differing head positions of the subject in the scanner and brain positions within the skull by reslicing one scan to match the other. As well as allowing better visual assessment of obvious changes, more subtle changes may become apparent. Registration allows better localization of atrophy than visual assessment alone and more precise measures of subtle changes. Registration can either be linear or non linear.

5.3.2.1.1. Linear registration

Several automated techniques have been designed to spatially match scans very accurately (Freeborough et al. 1996;Woods et al. 1998). These are based upon matching voxels of similar intensity (i.e., grey to grey voxels and white to white voxels) in the brain such that all structures approximate to corresponding structures on each scan of a registered pair. The basic registration process described by Freeborough et al (Freeborough et al. 1997) requires segmentation of the brain to remove non brain tissues

(the scalp and skull), then application of a number of rotations and translations to match the repeat scan to baseline. Three translations are applied in each direction within the x, y, and z-axis and three rotations around these axes produce a so-called six degrees of freedom registration (6 dof). The process can be extended to allow voxels to stretch and shear a small extent in each of the three planes (twelve degrees of freedom registration – 12dof). This theoretically allows for correction of inconsistencies in voxel size that may occur between the two scans. Once registered a difference image can be created, so that change between scans can be visualized.

Registrations can be performed on whole images or on smaller structures within the image following region delineation. Figure 5-4 shows the effects of linear registration of two scans of the same subject taken at different timepoints. For a review of technical details of these registration techniques see Ashburner et al (Ashburner et al. 2003).

Measurements can be obtained from each scan in a time series of scans using manual outlining or any of the other cross-sectional methods mentioned previously. Simply having scans registered before manual outlining can make significant improvements to the precision of measures, as arbitrary decisions based on anatomic boundaries may be more consistent.

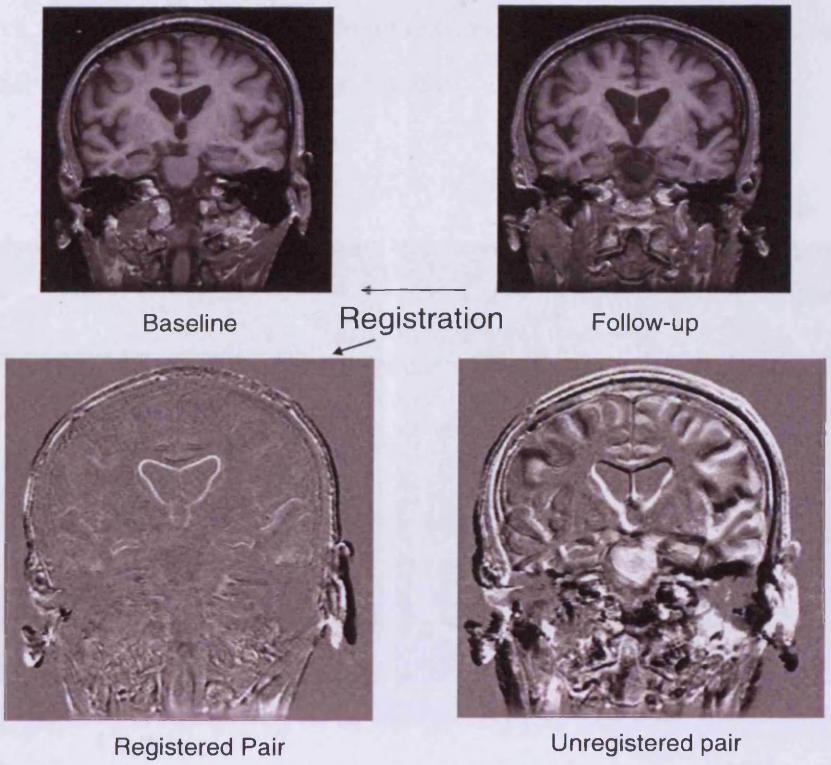
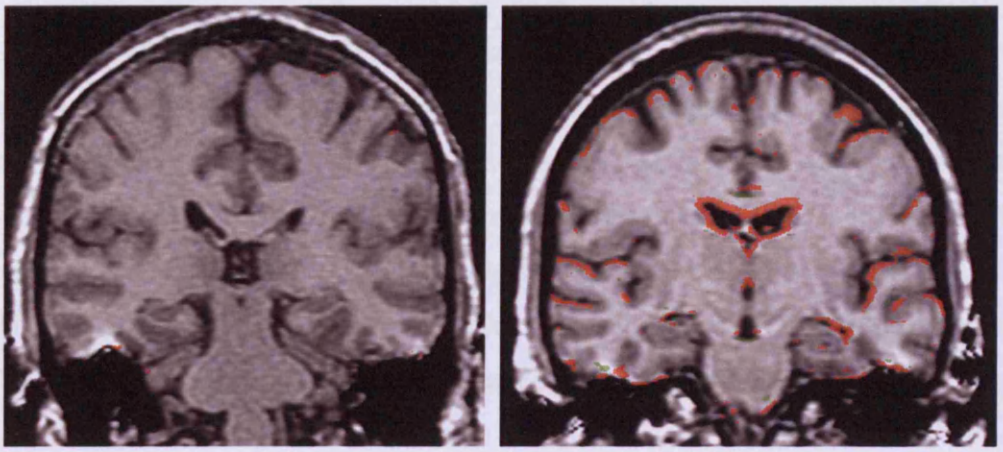


Figure 5-4 Difference images (baseline minus repeat)

Showing the effect of registration on real images by showing where the images do not correspond anatomically. Little of the brain structure is discernible in the registered image giving an overall grey appearance (no difference between the baseline and registered repeat). What is visible (a white outline of ventricles and some temporal gyri) represents loss due to atrophy between baseline and registered repeat image. By contrast in the unregistered scan pair, good matching has not been obtained and much of the mismatch is clearly visible (black and white areas).

The difference image (scan 1 subtracted from scan 2) can provide an accurate measurement of change in cerebral structure over time. One automated method for carrying out this direct measure of volume change is the brain boundary shift integral (BBSI). This has been validated as a robust and accurate measure of brain loss (Freeborough and Fox 1997). The BBSI calculates the change that has occurred at the boundary between the brain and cerebrospinal fluid at every point between the scans in each three-dimensionally registered scan pair. The change in intensity between the two scans at this border is quantified as brain loss or gain. This change can be visualized by colour overlays showing areas of loss or gain of brain tissue. Although this allows quantification of loss, localizing the exact position of this loss is not possible. Loss visualized at the border of the brain may mean loss of grey matter directly below the border, or alternatively, from the white matter structures at some distance from the

border. Nonetheless, these techniques give an indication of different patterns of loss (e.g., AD vs. Frontotemporal lobar degeneration (FTLD)) and a quantification of global and regional measurement of volume change.



Control AD

Figure 5-5 Measuring cerebral atrophy in registered serial MR imaging using the BBSI

The colour overlay shows increased cerebral atrophy and expansion of the ventricles over 1 year in the subject with AD as compared to the control. (Red shows areas of tissue loss)

5.3.2.1.2. Measuring change in focal areas

In addition to measuring whole brain atrophy over time, it is possible to detect focal changes longitudinally using manual segmentation by measuring smaller areas within the brain. This is useful, as throughout the course of AD, certain parts of the brain change more rapidly than others, e.g., hippocampi and entorhinal cortex. Measurement of these structures can allow differences to be seen between AD and normally ageing subjects at an earlier stage (Ridha et al. 2006). However, many of these measurements have an inherently higher level of measurement error compared with those of the whole brain. This is due to the difficulty in obtaining reproducible anatomical localization and delineation of these structures, and consequent standardization of segmentation protocols. As a result of the high measurement error and labour-intense processes needed for local segmentations, several semi-automated techniques have also been

developed for these regions that can measure change over time(Barnes et al. 2004;Crum et al. 2001).

5.3.2.1.3. Non-linear registration

As linear registration is unable to localize atrophy to specific tissues, non-linear techniques were developed not only to assess how much change occurs between scans, but also to determine from which tissues this loss has occurred. Such non-linear techniques, often referred to as tensor-based morphometry (TBM), are usually applied following some degree of linear spatial matching as described above. These techniques model brain changes in different ways, for example, as a viscous compressible fluid (Christensen et al. 1996;Freeborough and Fox 1998), or as elastic material (He and Christensen 2003). Application of these techniques can provide a colour overlay on the MR image, which can show areas where expansion or contraction of tissues has occurred. This is sometimes called a voxel compression map (see Figure 5-6). In theory, rates of volume change can then be directly calculated for any region of interest identifiable on the scans.

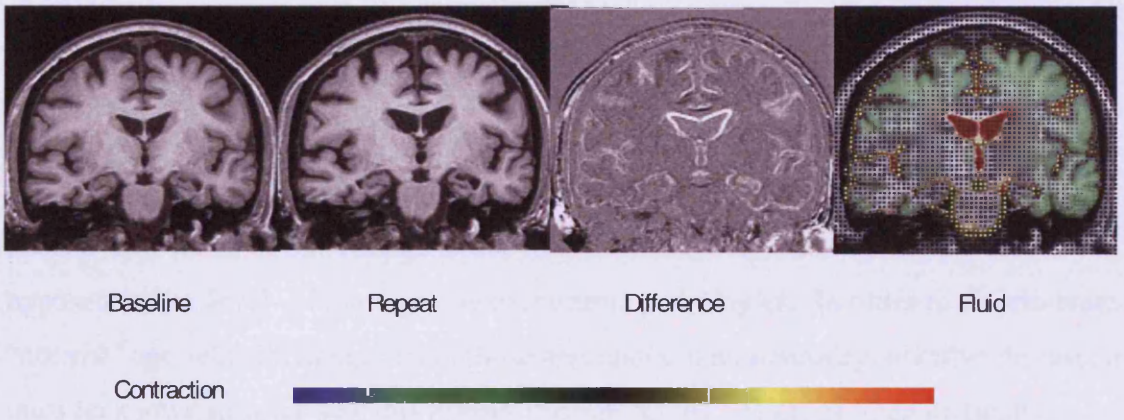


Figure 5-6 Baseline, linearly registered repeat, difference image and voxel compression map created from fluid registration of the two registered scans of an AD subject.

The coronal view is shown.

5.3.2.1.4. Other techniques for longitudinal image analysis

Voxel-based morphometry and cortical mapping, mentioned earlier in the text (see section 5.3.1.4), can also be used to analyse change in study groups over time (Scahill et al. 2002;Thompson et al. 2003).

5.4. Neuroimaging as a marker for early neurodegenerative disease

5.4.1. Cross-sectional imaging studies

The changes found on neuroimaging in early AD are well documented with atrophy first seen in medial temporal substructures such as the hippocampi and entorhinal cortex (ERC). Much attention has focused on how early these changes can be detected, and whether these changes can be identified in the absence of any clinical signs of the disease process. This next section evaluates both the cross-sectional and longitudinal studies that have been carried out to assess the role that structural neuroimaging has to play in detecting presymptomatic AD.

5.4.2. Longitudinal MRI changes and early neurodegenerative disease

5.4.2.1. Normal ageing

Cerebral structures change over time as a result of apparently healthy ageing. It is unclear how much of this change is due to an inevitable intrinsic ageing process as opposed to low levels of damage due to multiple pathologies. In order to discriminate "normal" age-related changes from those associated with neurodegenerative disease, it must be known in what way this normal change occurs. There is often difficulty, however, in defining a cohort that reflects the 'normal population'. Study cohorts vary regarding cognitive ability, vascular risk factors, and 'normal' scan appearances. Despite this, both cross sectional and longitudinal studies have shown that there are grey matter and white matter volume losses with ageing, with regional grey matter loss more prominent in the frontal and parietal regions (Good et al. 2001);(Resnick et al. 2000;Scahill RI et al. 2003). The relationship between ageing and cerebral atrophy is

non-linear, with certain regions of the brain changing at different times to others. Rates of global atrophy of 0.2% a year at age 30-50 and of 0.4% at age 70-80 have been reported in very healthy subjects (Fox et al. 2000;Jack, Jr. et al. 2004;Jack et al. 2000;Wang et al. 2002). Likewise hippocampal atrophy rates increase from around 0.1–0.2% a year in those aged 30–50, to 0.8% in those in their mid-70s, rising further to 1.5–2% a year at 80–90 (Fox and Schott 2004;Jack et al. 2000). Both this pattern and non-linearity of atrophy has been supported by work using cortical mapping techniques (Sowell et al. 2004).

5.4.2.2. Changes in presymptomatic familial Alzheimer's disease

Similarly to neuropsychological studies, neuroimaging work in presymptomatic familial AD (FAD) subjects has shown that changes in brain structure are detectable prior to the appearance of clinical signs. Serial MR scanning of individuals within 5-8 years of the historical onset of the disease has shown that significant hippocampal atrophy is demonstrable compared to healthy controls (Fox et al. 1996). Registration of serial MRIs in these FAD subjects showed that rates of atrophy increased at an early stage prior to the onset of measurable cognitive deficit, with a median rate of global atrophy of 1.0% per year (95% CI 0.78–1.88)(Fox et al. 2001). Schott et al measured medial temporal lobe atrophy (MTL) in their series at 5.74 % per year (95% CI 3.62 -7.83). Extrapolation of these rates of atrophy backwards in time suggested that these changes commenced 3.5 years before symptom onset (Fox et al. 2001;Schott et al. 2003). When these FAD subjects became symptomatic (yet still not fulfilling criteria for AD), there were increased rates of atrophy seen in the inferolateral temporal lobe, parietal lobe and posterior cingulate(Fox et al. 2001).

These findings suggest that structural changes in the medial temporal lobe can be detected in subjects with FAD at a stage before they become symptomatic. Care, however, must be taken before making direct comparisons between FAD and sporadic AD, as individuals with FAD have an earlier age of disease onset and often different clinical features to those with sporadic AD. Work carried out in early sporadic AD suggests that a similar picture may be present, as described below.

5.4.2.3. Amnestic MCI and presymptomatic sporadic AD

Earlier cross sectional studies showed that MTL changes were one of the first changes seen in sporadic AD. In 1989 de Leon et al published the first study showing that qualitative estimates of hippocampal atrophy in memory impaired subjects predicted decline to AD (de Leon MJ et al. 1989). Subsequent studies have also shown that in subjects with MCI, small baseline hippocampal size is predictive of future conversion to AD (Jack et al. 1999). The ERC has also been implicated early in the disease process. Du et al (Du et al. 2001) found that ERC and hippocampal volume measurements were significantly reduced in MCI subjects compared to controls with the magnitude of ERC atrophy similar to that of the hippocampus. Indeed some have found the ERC most reliably to differentiate MCI subjects from controls (Killiany et al. 2002). Others have found the hippocampus a better measure (Du et al. 2001) or of equivalent value (Xu et al. 2000).

Longitudinal studies have shown that rates of atrophy may be predictive of future cognitive impairment in 'normal' individuals. Rusinek et al in a 6-year longitudinal study demonstrated that MTL atrophy could predict which individuals with normal baseline cognitive functioning would convert to a diagnosis of MCI. The overall accuracy of the MTL prediction was 89% with a specificity of 94% and sensitivity of 77% (Rusinek et al. 2003). This suggests that, similarly to FAD, there is a stage at which cerebral atrophy is taking place when clinical signs may not be apparent. Another study demonstrated that over a period of three years significantly greater hippocampal atrophy had occurred in a group of control subjects who became cognitively impaired, and MCI individuals who progressed to a diagnosis of AD, than those who remained cognitively stable (Jack et al. 2000). The rates of atrophy of the control-converter (converting to MCI) and MCI-converter (converting to AD) subjects were comparable to those of the AD cohort. The rates of change of stable MCI subjects (no progression to AD) were similar to those of stable normal subjects, indicating that MRI measures of change correlated more closely with disease progression than with disease stage at baseline. This study also implied that the rate of hippocampal atrophy increases prior to the MCI stage but then seems to stay constant (at around 4% per year) as MCI progresses to established AD.

There has been some debate as to whether medial temporal lobe structures or measures of whole brain atrophy or ventricular size most closely correlate with disease progression. Measures of ERC atrophy provide an early and specific marker of AD, but measurement reproducibility can be affected by methodological difficulties such as reliably distinguishing the ERC region, often made more problematic by poor grey or white matter differentiation on scans. Measurements of hippocampal change are sensitive as an imaging marker of AD, and with the development of semi-automated measurement techniques, often simpler to identify and measure (Haller et al. 1996). These measurements also have their drawbacks as although a relatively sensitive marker of AD, hippocampal atrophy is not entirely specific to Alzheimer's disease. Significant atrophy of the hippocampus (especially anteriorly) is recognized as a characteristic of frontotemporal lobar degeneration.

One investigative group compared hippocampi, entorhinal cortex, and whole brain atrophy rates and rates of ventricular expansion and found that whole brain atrophy and changes in ventricle size correlated most strongly with disease progression (Jack et al. 2004). A further structure, the cingulate gyrus, has been postulated as a specific marker for disease progression from MCI to AD, preceding the alteration of executive functions and tending only to be neuropathologically affected in clinically probable AD (Chetelat and Baron 2003). Killiany et al found in their longitudinal study that baseline anterior cingulate volumes best differentiated individuals with 'questionable dementia' (i.e. mild memory problems) and those who had converted to a diagnosis of AD three years later (Killiany et al. 2000).

Volumetric MRI measures of cerebral atrophy are free from subjective effects such as motivation, general health, anxiety, depression or fatigue that may contribute to cognitive test and rating scale variability. Where it is uncertain if an individual reaches criteria for Mild Cognitive Impairment or other diagnosis, MRI provides an objective measure of disease, allowing greater clinical certainty and potentially providing information regarding prognosis. Furthermore, information from neuroimaging (MRI measures of MTL atrophy) and neuropsychological assessments in combination has proven beneficial, providing a high predictive value for progression to AD (Arnaiz and Almkvist 2003;Petersen et al. 2001).

Similarly to neuropsychological studies, prospective MR imaging studies of individuals thought to be at high risk for AD are limited by group heterogeneity. Where multiple underlying pathologies are present they will dilute any observed changes attributable to early AD. Therefore in a study of early AD it is important that subject selection excludes those that may have memory complaints secondary to other causes such as strategic infarcts or psychiatric factors.

5.5. Positron emission tomography

Positron Emission Tomography (PET) uses radioactively labelled tracers to evaluate brain function. A short-lived radioactive tracer isotope, chemically combined with a metabolically active molecule, is injected into the patient. Once concentrations of the molecule have built up sufficiently within the tissues of interest, the patient is placed in the PET scanner. As the isotope decays it emits a positron, which then after travelling less than a millimetre is annihilated by a negative electron. As a result two photons are emitted simultaneously which move in opposite directions. These are detected by the positron camera surrounding the patient, which is composed of photomultiplier tubes. When the photons enter the detectors simultaneously they produce a pulse. Single photons of background radiation entering only one detector are ignored and not counted. The scanner uses the pair-detection events to map the density of the isotope within the body. This map shows the tissues in which the molecular probe has become concentrated. Limitations to this method of imaging include the high costs of cyclotrons needed to produce radionucleotides for PET scanning and the short half lives of radiotracers which limit the distance that they can be transported to PET scanners.

Using different radioactive tracer isotopes, PET can show patterns of blood flow and metabolism of oxygen or glucose. Altered metabolism of glucose occurs in different neurodegenerative diseases with decreased temporoparietal uptake of labeled glucose (F-18 fluorodeoxyglucose - ^{18}FDG-PET) found in AD. Although changes in ^{18}FDG have also been found in the earlier stages of AD, ^{18}FDG-PET remains most sensitive and specific for moderate to severe cases of dementia. In recent years, however, new ligands have been developed to image the amount and distribution of amyloid in the brain. These amyloid binding agents are lipophilic and have good blood brain barrier permeability and clearance from the brain (see Sair et al for review(Sair et al. 2004)).

One thioflavin based radioligand ^{11}C-PIB (*N*-methyl-[^{11}C]2-(4′-methylaminophenyl)-6-hydroxybenzothiazole, Pittsburgh Compound-B) has recently been shown to demonstrate amyloid deposition within the brains of APP transgenic mice (Bacskai et al. 2003) and in a cohort of subjects with mild AD(Klunk et al. 2004). Other agents are also being investigated, with an amyloid and neurofibrillary tangle binding ^{18}F-FDDNP (2-(1-(6-[(2-[18F]fluoroethyl)(methyl)amino]-2-naphthyl)ethylidene)malononitrile) also demonstrating increased retention in the temporal, parietal, frontal, occipital cortices and the hippocampal, amygdale and entorhinal regions (Shoghi-Jadid et al. 2002).

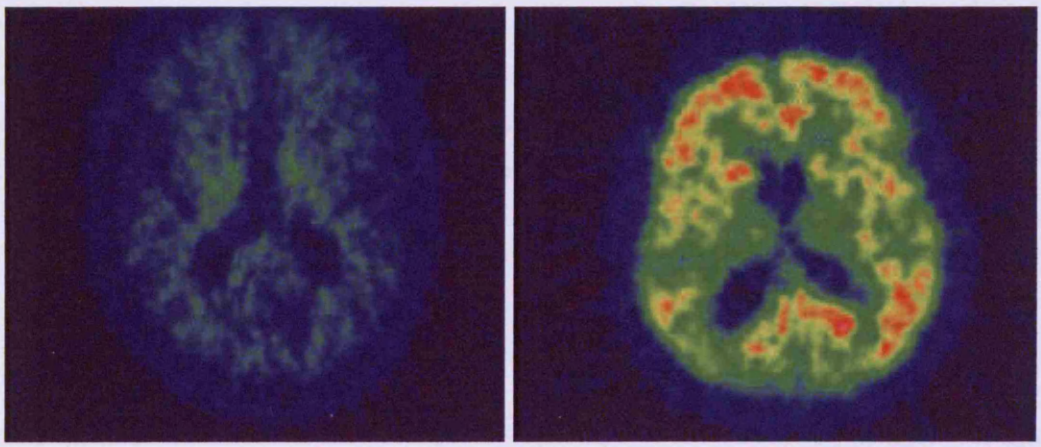


Figure 5-7 ^{11}C-PIB PET image of a control and AD subject

Increased uptake of ^{11}C-PIB is seen in the subject with AD reflecting increased binding to cerebral amyloid.

5.6. Summary

Advances in neuroimaging over the last decade have made it possible to visualise the pattern of cerebral atrophy that takes place in AD. Work in both presymptomatic familial and sporadic AD has shown that changes in the medial temporal lobe and its substructures, the hippocampi and entorhinal cortex, can be present before clinical signs of disease are detectable. However, the use of MR imaging in neurodegenerative disease does have its limitations; although these changes may be sensitive for AD they are not always specific as there is an overlap between brain appearances in normal

ageing and AD, as well as with other neurodegenerative diseases. Changes in the cingulate may provide a marker for progression to AD, and confer more specificity on the diagnosis. Other limitations include availability, cost, and the need for operator expertise and consistency. Similar to the neuropsychological assessment of preclinical AD, serial assessments using the patient as his own control are required to monitor disease progression and to be certain of a diagnosis of AD. Whilst both neuroimaging with MRI and neuropsychological testing alone provide information on a disease process a combination of these two modalities provides an even greater sensitivity and specificity for a diagnosis of AD. With the added combination of ^{11}C-PIB PET, able to detect the histopathological hallmarks of AD, the sensitivity and specificity of early diagnosis will likely improve.

5.7. Conclusions to the introduction and questions

5.7.1. Conclusions

Identifying individuals at an early stage in Alzheimer's disease is important. Changes in the brain can occur up to 20 years prior to a diagnosis of AD being given. With potentially disease modifying therapies becoming available in the future, early identification of individuals at risk of developing AD is a clinical priority to allow early initiation of treatment.

Symptoms of memory loss may be related to future cognitive impairment and can be one of the first signs of the presence of neurodegenerative disease. Their usefulness as a marker of early AD is limited, however, by their association with other disease processes as well as normal ageing. Neuropsychology and neuroimaging have also been shown to be sensitive to the early changes of neurodegenerative disease.
The ability of previous studies to identify those at risk of AD has been limited by choice of cohort and investigation method. In view of these limitations this thesis will undertake analysis in a cohort that is free of other psychiatric or physical illness that can also result in symptoms of memory loss, use a robust neuropsychological assessment at baseline to ascertain baseline cognitive status and use a clinically derived, referred or self-referred study cohort.

5.7.2. Questions

This thesis aims to:

(1) Critically assess whether symptoms of memory impairment in a clinical setting predict future cognitive impairment
(2) Assess how best to differentiate individuals with AD from those ageing normally, where symptoms of memory loss are very common within the general population.
(3) Critically assess whether annual neuroimaging and neuropsychological assessments can predict future cognitive decline
(4) Critically assess the relative merits of history taking, neuropsychological assessment and neuroimaging in prediction of future cognitive impairment,
(5) Assess whether annual follow-up of individuals with memory complaints is an appropriate period over which to see changes in cognition and neuroimaging.
(6) Provide clinically useful information for those referring patients to and working in memory clinics, for example, on whether to initiate treatment or not, or how to plan follow-up for these individuals
(7) Provide more information on the natural history of early AD.

6. Methods

6.1. Pre MCI longitudinal study - study overview

This study follows a cohort of individuals with amnestic mild cognitive impairment (aMCI) and symptoms of memory loss but normal general cognitive function (SNCI), and healthy volunteers for two years. At each annual visit a clinical and neuropsychological assessment were carried out and all subjects had a volumetric MR scan of the brain. The rate of cerebral atrophy and any decline in cognitive functions were calculated using the baseline and year one neuroimaging and neuropsychology data. These measurements were then used to predict which subjects would show a clinical decline over the two-year follow-up period.

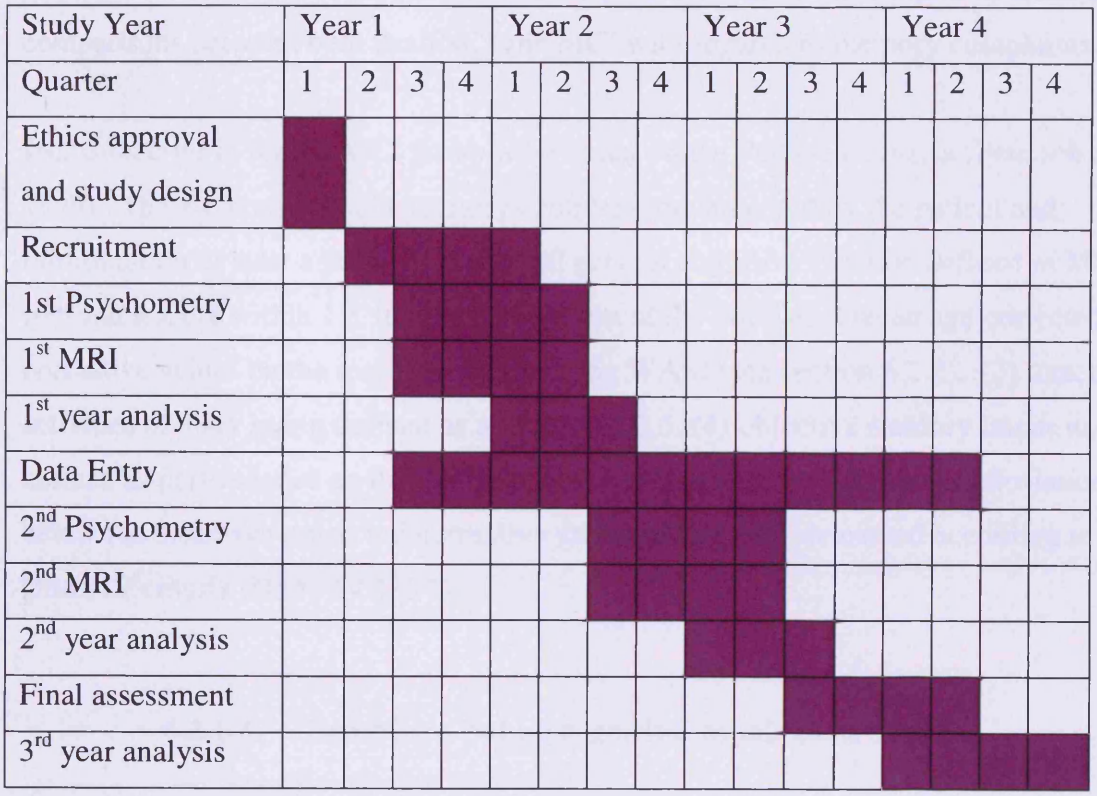


Figure 6-1 Time scale of the Pre MCI longitudinal study

6.2. Subjects

6.2.1. Subject selection and inclusion criteria

We aimed to recruit in the region of 25 subjects with MCI, 35 subjects with SNCI and 30 healthy volunteers (see power calculation section 6.7). To restrict the focus of the study to individuals at risk of developing AD, all subjects had to be between 49 and 86 years of age. The inclusion criteria for each of these three groups are outlined below and in Table 6-1.

6.2.1.1. Mild cognitive impairment (MCI)

The Petersen Criteria (Petersen et al. 1999) were chosen for this study, as they were a well validated and commonly used set of criteria for mild cognitive impairment. In addition, unlike a number of other criteria, they specified not only the level of memory impairment, but required the presence of memory symptoms allowing us to make direct comparisons between both the SNCI and MCI with regards to memory complaints.

Inclusion criteria for the MCI group were based on the Petersen Criteria (Petersen et al. 1999). These comprised: (1) memory complaint documented by the patient and informant for at least a year, (2) preserved general cognitive function defined as MMSE >26 and a score within 1.5 standard deviations of the published mean age-corrected normative values on the matrices subset of the WASI (see section 6.2.2), (3) intact activities of daily living defined as a CDR of ≤ 0.5, (4) objective memory impairment, defined as performance on the CVLT or RMT at greater than 1.5 standard deviations below the mean age-corrected normative values and (5) not demented according to DSM-IV criteria (DSM-IV 1994).

6.2.1.2. Symptoms but no cognitive impairment (SNCI)

Inclusion criteria for the SNCI group were: (1) memory complaint documented by the patient and collateral source for at least a year, (2) preserved general cognitive function defined as MMSE >26 and a score within 1.5 standard deviations of the published mean age-corrected normative values on the matrices subset of the WASI, (3) intact activities of daily living defined as a CDR of ≤ 0.5, (4) no objective memory impairment (as

previously defined in 6.2.1.1) and (5) not demented according to DSM-IV criteria (DSM-IV 1994).

6.2.1.3. Healthy volunteers

Inclusion criteria for the healthy volunteers were: (1) no cognitive complaint, (2) preserved general cognitive function defined as MMSE >26 and a score within 1.5 standard deviations of the published mean age-corrected normative values on the matrices subset of the WASI and (3) no objective memory impairment (as previously defined in 6.2.1.1). Where possible, controls were spouses of patients participating in the study who were recruited for practical reasons and to aid accurate matching of the groups in terms of background, age and education.

6.2.2. Normal general cognition

As outlined previously (see section 2.6.2), there is no standard definition for normal general cognition and the criteria used show wide variations. To define normal general cognition for the purpose of this study, a departmental consensus meeting was held with substantial input from both consultant neurologists and neuropsychologists. Our aim was to use a measure of functional activities, evidence from an informant, and cognitive tasks to define whether general cognitive function was intact, in line with the recommendations of the MCI consensus meeting in 2004 (Winblad et al. 2004).

Functional ability was assessed by a clinician administering the CDR. This rating was chosen because it has been widely used to assess individuals of 'pre dementia' states and in certain studies has been the chosen measure of cognition (Galvin et al. 2005). In addition the CDR provides information from both subject and informant. The matrices subset from the WASI, and the MMSE were chosen as appropriate cognitive tasks for assessing general cognition. The WASI matrices is a culturally neutral measure of IQ and a cut-off of performance of 1.5 standard deviations below age-corrected normative values was used to define impairment. This was in keeping with the 1.5SD cut-off on memory tests already stipulated by the Petersen criteria. The use of subtests of IQ measures to define normal cognitive function has also been used by other groups (Geslani et al. 2005). The MMSE is widely employed in research and clinical practice

as a test of general cognition. Several studies have used this in isolation (Storandt et al. 2002) whilst others have used an augmented version (e.g., the modified mini-mental state examination - 3MS (Tierney et al. 2005)), or combined it with another short screening test (such as the Short Blessed Test (Storandt et al. 2006)). In this study we used a score of less than 26 as an indication of impaired general cognition. Both the WASI matrices and MMSE were particularly suited to this study in view of the proportion of subjects who spoke English as a second language. Our resultant definition of normal general cognition fulfilled the recommendations of the 2004 consensus meeting and is summarized in Table 6-1.

Table 6-1 Study inclusion criteria

		MCI	SNCI	Controls
Age	49-86	Yes	Yes	Yes
Memory complaint >1year		Yes	Yes	No
Normal cognitive function	CDR	≥0.5	0	N/A
	MMSE	>26	>26	>26
	WASI matrices	>1.5SD	>1.5SD	>1.5SD
Intact activities of daily living		yes	yes	yes
Objective memory impairment	<1.5SD	yes	no	no
Demented		no	no	no

6.2.3. Exclusion criteria

Exclusion criteria were the same for all subject groups and were aimed at excluding any individuals with an obviously identifiable or treatable cause for their memory loss, or who had a contra-indication to MR scanning. They included:

(1) MRI findings that suggested:

(a) neoplasm, haematoma or cerebral haemorrhage

(b) white matter change to be compatible with MRI criteria for vascular dementia (25% of total white matter)

(c) strategic cerebral infarction (NINDS-AIREN criteria National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale

pour la Recherche et l'Enseignement en Neurosciences (AIREN))(Roman et al. 1993),

(2) Any significant disease or unstable medical or psychiatric condition that could influence neuropsychological testing. History of schizophrenia, schizoaffective disorder, bipolar disorder or having had electroconvulsive therapy (ECT),

(3) Current or recent history of drug or alcohol abuse/dependence or treatment with sedatives, neuroleptics or anxiolytics,

(4) Participants in whom magnetic resonance imaging (MRI) was contraindicated or impracticable eg: claustrophobia or cardiac pacemaker.

6.2.3.1. White matter disease exclusion

To restrict the focus of this study to that of AD and preclinical AD, our exclusion criteria aimed to omit individuals who might have had another cause for their cognitive complaints, such as vascular disease. As there is no clear relationship between the amount of vascular disease seen on MRI and vascular dementia, we chose a cut-off of 25% of white matter change to identify and exclude individuals in whom it would seem likely that vascular disease was in part responsible for their memory complaints. This number was chosen based on the NINDS-AIREN report on vascular dementia by Roman et al 1993 (Roman et al. 1993) and referred to more recently by Guermazi et al (Guermazi et al. 2006). Strategic infarctions refer to the clinical syndromes resulting from small, localized ischaemic damage in functionally important cortical and subcortical areas. They include angular gyrus infarcts and thalamic infarcts (Roman et al. 1993). Application of these last two exclusion criteria resulted in the exclusion of two male individuals from the study cohort, aged 77 and 83 respectively. They both would have fulfilled criteria for the SNCI category and did not otherwise differ from the final sample.

6.2.4. Consent and ethics

All participants were given an information sheet to read prior to recruitment to the study and informed consent was obtained at the study visit itself. This study had ethics approval from the National Hospital for Neurology and Neurosurgery joint ethics committee. Involvement in this study was voluntary and participants were able to

withdraw at any time. Travel expenses were reimbursed, and refreshments provided if participants had travelled a long distance. All subjects signed consent for their data to be stored under the Data Protection Act.

6.3. Study design

An overview of the study is given in Figure 6-1.

6.3.1. Clinical assessment

6.3.1.1. Clinical assessment prior to enrolment

All MCI and SNCI subjects were assessed by a clinician prior to referral to this longitudinal study. Assessment at the NHNN included baseline blood tests e.g., thyroid function tests, syphilis serology, full blood count, urea and electrolytes, liver function tests, erythrocyte sedimentation rate, and autoimmune screen. A baseline chest radiograph, electrocardiogram and standard neuropsychological assessment were also performed. In addition patients had an electroencephalogram and magnetic resonance imaging of the brain. Initial investigations performed by linked memory clinics closely paralleled those of the NHNN, although not all clinics performed electroencephalograms or, neuroimaging.

6.3.1.2. Clinical assessment at study visit

All subjects were assessed annually over a three-year period. At the baseline visit a detailed history of symptoms was taken from the subject and the informant. The subject and informant were asked independently how the subject's memory compared with that of other individuals of a similar age and were requested to describe the nature of the memory loss. Specific questions regarding memory functions, activities of daily living and affective symptoms were recorded using the validated questionnaires as described below and in Appendix 7. Enquiries were also made about any changes in other cognitive functions or behavior. Medical history, extent of formal education, vascular

risk factors, drug history and current medication were recorded on a data sheet. Handedness was also established. Each subject underwent a protocol-led physical and neurological examination including measurement of blood pressure by a clinician (HA) (see Appendix 6).

Relatively few subjects with depression were referred for this study as those with depression as a cause for their memory symptoms tended to be treated by the referring health professional instead. However presence of depression was assessed in all subjects through taking a full clinical history and where subjects were currently being treated for depression or had had a past history of electroconvulsive therapy (ECT) they were excluded (resulting in exclusion of one subject due to past ECT). To achieve a formal rating of any depressive symptomatology, all subjects were asked to complete the geriatric depression scale (see section 7.1.3.2).

6.3.1.3. Questionnaires

Four questionnaires were utilized in this study to assess memory complaints, daily functioning, depression and anxiety:

The Memory Functioning Questionnaire

Subsequent to enrolment to the study, subjects and their informants were given the Memory Functioning Questionnaire (MFQ) (Gilewski and Zelinski 1988) to complete. This questionnaire consists of 4 subscales designed to assess frequency of forgetting, seriousness of forgetting, impression of past performance and memory stratagems. Subjects and informants rated the subject's memory according to a 7-point rating system, where a score of 0 indicated constant difficulty with a particular task and a score of seven no difficulty. Memory aid ratings were also based on a scale of one to seven with one reflecting routine use of an aid and seven indicating that it was never employed. Memory aids specifically enquired about were reminders lists, calendars, diaries, mental repetition and planning in advance. The total score from the frequency of forgetting and memory stratagem subscales were calculated for each individual and used in the analysis.

The Clinical Dementia Rating

The Clinical Dementia Rating (CDR)(Morris 1993) is a 5-point scale used to assess memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Information from a semi-structured interview with the subject and their informant is used to score each domain. The resultant score indicates how well an individual is functioning on a daily basis and based on this they are assigned a rating of either no dementia (CDR=0), questionable dementia (CDR=0.5), mild dementia (CDR=1), moderate dementia (CDR=2) or severe dementia (CDR=3).

The Geriatric Depression Scale

The Geriatric Depression Scale (GDS)(Sheikh VI and Yesavage VA 1986) is a screening tool for identifying depressive symptoms in older adults. The shortened form of this questionnaire contains 15 questions. Scores of 0-4 suggest no depression, 5-10 mild depression and 11 or greater, severe depression.

The Clinical Anxiety Scale

The Clinical Anxiety Scale (CAS)(Snaith et al. 1982) is a rating system with a maximum score of 24. Subjects are asked how they have felt over the last two days with regards to psychic tension, ability to relax, startle response, worrying, apprehension and restlessness. An increase in score reflects an increase in anxiety. In this study we shortened this questionnaire to an abridged form with a maximum score of 20. Five subjects had this score derived retrospectively from similar anxiety questions using the Clinician interview-based impression of change (CIBIC) (Schneider and Olin 1996). Comparison of group anxiety ratings including and excluding scores of these individuals did not differ significantly (MCI and SNCI combined p=0.6, MCI p=0.9, SNCI p=0.6).

6.3.2. Neuropsychological assessment

6.3.2.1. Choice of neuropsychological battery of tests

A neuropsychology battery was administered by a trained neuropsychologist to all subjects at each study visit. Details of the battery are given below. In brief, assessments were made of estimated premorbid IQ as well as current IQ, and tests were administered to assess the following domains: verbal memory; visual memory, vocabulary, reasoning/executive function; naming and visuoperceptual skills. A particular emphasis was made on inclusion of tests that would be sensitive enough to detect an early change in memory. The battery was chosen to allow comprehensive testing of the cohort, but of a duration that would not result in patient fatigue. Despite this intention, the battery had to be modified shortly after the study began to decrease the length of cognitive testing from two to one and a half hours. This included substituting the matrices and vocabulary subsets of the Wechsler Abbreviated Scale of Intelligence (Gilewski and Zelinski 1988)(WASI) for the Wechsler Adult Intelligence Scale (WAIS)(Wechsler 1981). This was mainly for reasons of patient fatigue and the overall IQs were thought to be generally comparable. Where the WAIS-R had been administered prior to the WASI, the score from the performance IQ of the WAIS-R was used as the equivalent test to the matrices subset of the WASI.

6.3.2.2. Neuropsychological battery

The National Adult Reading Test (NART)(Nelson and Willison 1991) and the matrices and vocabulary subsets of the WASI were used as tests of verbal and performance IQ, the Graded Naming Test (GNT)(McKenna and Warrington 1983) as a test of naming ability, the California Verbal Learning Test (Delis et al. 1987) to test verbal learning and memory, and the Warrington Recognition Memory test (RMT)(Warrington 1984) to evaluate verbal and non verbal learning and memory, the Silhouettes subset of the Visual Object and Space Perception Battery (VOSP)(Warrington and James 1991) to assess object and space perception, and the Trail Making Test (TMT)(Delis D.C. and Kaplan E. 2001) to evaluate visual conceptual and visuomotor tracking and allow assessment of psychomotor speed and attention.

To align this study with the assessment of mild cognitive impairment subjects carried out at other sites, copy, recall and delayed recall of the complex Rey-Osterreith figure

(ROF)(Osterrieth PA 1944) were added just after the start of the study. This provided an additional measure of visual memory.

6.4. Magnetic resonance imaging

6.4.1. Acquisition

The protocol chosen (MIRIAD) was based on that utilized in previous longitudinal studies of volumetric imaging in AD (Schott et al. 2005). This included T1 volumetric, axial proton density / T2 weighted dual echo fast spin echo and coronal FLAIR images. This protocol was chosen as it had a high signal to noise ratio (SNR) and minimum distortion, shading and susceptibility artifact. It offered high contrast between grey matter and cerebrospinal fluid (CSF) and between grey matter and white matter. It allowed anatomical accuracy and ease of outlining using the Medical Information Display and Analysis System (MIDAS) semi-automated segmentation tool, and had no adverse effect on the BBSI.

All MRI Imaging was performed using the same 1.5 Tesla General Electric scanner. T1-weighted volumetric images were obtained using an inversion-recovery prepared fast-spoiled Gradient Recalled Acquisition at Steady State (GRASS)(IRpFSPR) sequence technique with a 28-cm field of view and 256 x 256 matrix to provide 128 contiguous 1.5-mm-thick slices in the coronal plane. The scan acquisition parameters used were repetition time = 15ms, echo time = 5.4 ms, flip angle = 15° and inversion time = 650ms. The length of time to acquire a volumetric scan was just over 10 minutes. Subjects were reminded to remain as still as possible during the scanning and were given earplugs to avoid excessive noise. All subjects were able to communicate with the radiographer during the course of the scan.

All MR images were visually assessed and clinically reported by a consultant neuroradiologist blinded to the clinical details of the subject. Hippocampi were reported as being either small or large. Intraobserver agreement of hippocampal size was 87%, correcting for chance agreement, kappa was 67%.

After acquisition, digitised images were transferred to a Linux workstation for analysis.

6.4.2. Processing of MRI scans

Image intensity inhomogeneity or bias is the slowly changing and smooth spatial variation in signal intensity that can occur within the scan. This artefact may be caused by several factors: inhomogeneity of the magnetic field, inhomogeneity of the radiofrequency pulse or non-uniform sensitivity of the receiver coils used to detect the MR signal. This bias has implications for downstream processing, as segmentation of images and registration of images can be affected. In order to correct for this potential inhomogeneity in the images, all were bias corrected using the N3 correction algorithm prior to scan registration and the differential bias correction (DBC) algorithm post scan registration (Lewis and Fox 2004;Sled et al. 1998). Further image processing was performed using the MIDAS software tool (Freeborough et al. 1997). Whole brain segmentation was achieved through using a semi-automated technique, with interactive intensity thresholding used to identify voxels within the brain. A series of erosions and dilations were then applied to delineate brain tissue from surrounding tissue, such as scalp and dura (see Appendix 8). Brain volumes for each scan were calculated directly from the MIDAS software tool, with a single measurement TIV to provide cross-sectional correction (Whitwell et al. 2001) (see Figure 6-2).

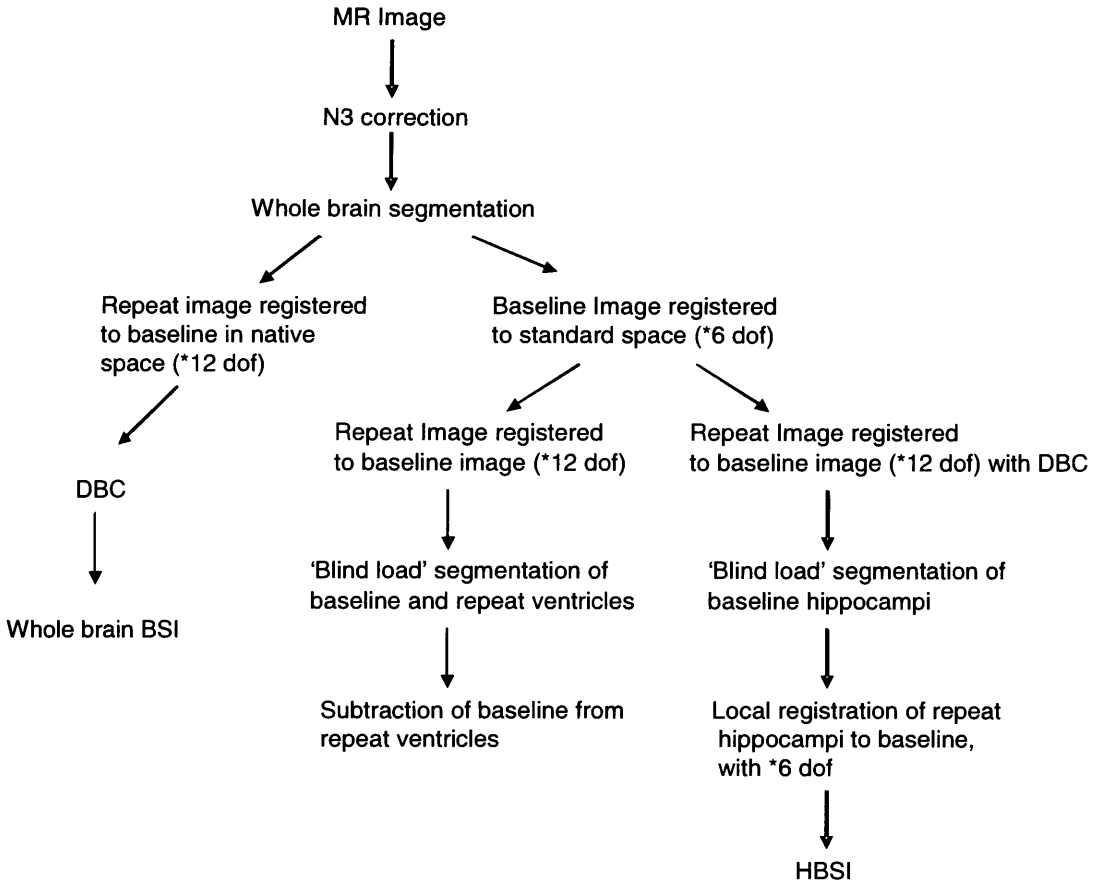


Figure 6-2 Flow chart to show the different processing steps used to obtain volumes and rates of atrophy or enlargement for whole brain, ventricles and hippocampi

***6 degrees of freedom (dof) (rigid) registration involves rotations and translations in the x, y and z axes of the image. To remove fluctuations in voxel size and improve spatial matching of the images, further shears in the x, y, and z planes can be added to a 9 dof (rigid plus scaling) registration to make a 12 dof (affine) registration**

To calculate ventricular volumes, images were first registered to the Montreal Neurological Institute (MNI) 305 brain average (Mazziotta et al. 1995), using a 6 degrees-of-freedom registration. To avoid problems with voxel drift each scan pair was then co-registered by registering the repeat scans to the baseline image using an affine (12) degrees-of-freedom registration (Woods et al. 1998). Ventricular volumes were outlined by HA using a semi-automated technique from the MIDAS package on the baseline and repeat images for each subject. An upper threshold of 60% of mean brain region intensity was used. Ventricular volumes included the lateral ventricles and temporal horn of the lateral ventricles but not the third or fourth ventricle and were outlined on all sequential brain slices encompassing these regions (see Appendix 9). Intra-rater reproducibility was greater than 99.5%.

For hippocampal-volume measurements, all scans were registered as before, to the MNI standard brain template using a six-degrees-of-freedom algorithm to reduce any variability in landmarks used in delineating the hippocampus and ensure all images were in a similar orientation (Mazziotta et al. 1995). Each baseline hippocampus was manually outlined by an experienced rater (TP, intra-rater reproducibility 95%) with multiple views to include the cornu ammonis, gyrus dentatus and subiculum (Scahill RI et al. 2003). The hippocampus was always measured on the right hand side of the presented image with the investigator blinded to the subject's name, diagnosis, chronological order, and left–right orientation of the scans. We calculated left, right, and total (left+right) hippocampal volumes. Both hippocampal and ventricular volumes were segmented with the segmentor blind to any clinical details and date of image acquisition ('blind load').

6.4.3. Rigid–body registration, the BBSI and rates of atrophy

To allow accurate comparisons between serially acquired scans, affine registration was performed using the AIR 5.2 package as described by Woods et al (Woods et al. 1998).

Calculation of whole brain atrophy from the registered scan pairs was performed using the brain boundary shift integral (BBSI)(Freeborough and Fox 1997) (for theory see section 5.3.2). After registration of the baseline and repeat images this technique was used to calculate directly the volume of brain tissue lost over the entire 3D brain-CSF interface. Annualised rates of whole brain atrophy were then calculated as a percentage of the baseline brain volume for each scanning interval.

Rates of ventricular atrophy were calculated by subtracting the outlined regional volume on the baseline region from the repeat scan and expressed as volume change (ml) per year (Schott et al. 2005).

Changes in adjusted total hippocampal volumes were calculated by using the hippocampal BSI (Barnes et al. 2004).

6.4.4. WMH

WMH volume was quantified by applying local thresholding on whole brain proton density and T2-weighted images (1.5T MR scanner) using a semi-automated user dependent technique (Garde et al. 2005). Best reproducibility was achieved through using two raters (HA and EG) simultaneously to agree WMH, and this corresponded to an intra-rater correlation coefficient of 0.99.

6.5. Apolipoprotein E genotyping

Consent was obtained from all participants to carry out this procedure performed in the MRC Prion Unit University College London. Ten millilitres (ml) of blood was collected by venepuncture. DNA was extracted using standard techniques and Apolipoprotein (ApoE) genotyping was determined using a standard one-stage polymerase chain reaction (Wenham et al. 1991).

6.6. Follow up and outcome measurement

The total period of follow-up chosen for this study was two years. At each annual follow up visit the CDR and MMSE were repeated and any change in symptoms or clinical state recorded by the clinician (HA and JK). Repeat neuroimaging and neuropsychology were carried out in an identical fashion to that of the baseline visit. Rates of cerebral atrophy and change in neuropsychological scores were calculated from the baseline and year 1 data. We set two predetermined outcomes to this study, which are explained in detail in chapter 10. In brief, change in clinical status was the first outcome measure, as determined by progressive decline in neuropsychological performance over two years and clinical review by a senior neurologist. Our second measure was change in the sum of boxes score on the CDR over two years.

6.7. Statistics and power calculation

STATA version 8 (Stata Corporation, College Station, Texas 2003) was used to perform standard parametric and non-parametric tests which were used to investigate basic linear

and test group differences. Details of the exact tests employed can be found within the results sections.

Power calculations were performed using standard formulae (Armitage P 2002). The power calculation for this study was performed to estimate the number of subjects required to give the study 90% power to detect a difference in the rates of cerebral atrophy between the MCI and the control groups, and the SNCI and the control groups using a conventional p-value for statistical significance of 5%. They also allowed for a drop out rate of 10%. The actual drop out rate in this study was 3% over 2 years. The equation used is shown below:

$$(n1-n2)/\sqrt{(SD1^2/n1) + (SD2^2/n2)} > 1.96 + 1.282 = 3.242$$

Where n1 and SD1 are the mean and standard deviations respectively for the rates of cerebral atrophy in the MCI or SNCI groups (separate calculations carried out for each group). Correspondingly n2 and SD2 are the means and standard deviations for rates of atrophy in the control group. 1.96 is the 97.5^{th} percentile of the standard normal distribution, 1.282 is the 80^{th} percentile of the standard normal distribution.

The values for n1 and n2 were based on known rates of cerebral atrophy. According to Fox et al (Fox et al. 2000) the mean rate of cerebral atrophy for patients with AD is 2.37% (1.11%SD) per year, for healthy controls it is 0.41% per year (0.47%SD). Mueller et al (Mueller et al. 1998) suggest that healthy oldest-old subjects do not show greater rates of brain loss compared to younger elderly. We have estimated rates of brain atrophy in MCI using our own data to be 1.2 % (1%SD) and postulated that the rate of change in the SNCI group will be 0.8% (0.7%SD) based on presymptomatic FAD studies (Fox et al. 2001). Estimates from previous studies suggest amnestic MCI progress to AD at a rate of 10% to 15% per year compared with healthy control subjects who convert at a rate of 1% to 2% per year (Petersen et al. 1999;Tierney et al. 1996).

7. Results

7.1. Descriptive data

7.1.1. Introduction

This section describes the baseline characteristics of the healthy volunteers, SNCI and MCI groups enrolled into this study. The clinical, neuropsychological and neuroimaging data are each taken in turn. The aim of the work described in this chapter is to characterise these three groups and show their differences and similarities to each other at the baseline visit.

7.1.2. Data analysis

Methods are discussed in chapter 6. When comparing characteristics (e.g., vascular risk factors) between groups, t-tests were used if data were normally distributed. Variances were compared between groups using F-tests and the form of the t-test adjusted accordingly. Where data were not normally distributed the Wilcoxon rank sum test was used. A chi-squared test was used to compare proportions of patients with an ApoE4 allele.

7.1.3. Results

7.1.3.1. Recruitment

In total 99 subjects were recruited to this study over the period of one year. They were 34 healthy volunteers (CNTRL), 25 subjects with MCI and 40 SNCI. The MCI and SNCI subjects were recruited from the cognitive disorders clinic of the National Hospital for Neurology and Neurosurgery (NHNN) and its linked memory clinics. These included Northwick Park Hospital (NPH), Chelsea and Westminster Hospital

(CWH) and Welwyn Garden City Hospital (WGC). These subjects were referred from a variety of sources including both GP referrals and referrals from psychogeriatricians and neurologists (see Table 7-1). Healthy volunteers were either spouses or friends of study participants, or recruited using advertising within the NHNN and the Mary Ward Centre (a local further education college).

Table 7-1 Recruitment sources

Group	NHNN Clinic	Psychogeriatrician	Neurologist	Advert
SNCI	36	2	2	0
MCI	22	2	1	0
Controls	30	0	0	4

Following the screening visit, one individual was excluded due to claustrophobia, two due to extensive white matter disease, two due to a past history of ECT therapy, three due to cognitive impairment falling outside the boundaries defined for MCI, one outside the boundaries for SNCI and one due to lack of informant. The resultant eighty-nine subjects met study criteria and were enrolled into the study. They comprised 33 healthy volunteers (CNTRL), 21 MCI and 35 SNCI. Eleven of our study subjects (2 controls, 9 SNCI) had not been educated in English until after the age of eleven, although all could converse easily in English. The proportion of subjects of non-English speaking origin in this study cohort is not dissimilar to the proportion of non-English speaking patients routinely seen in outpatient clinics at the NHNN. Countries of origin were Venezuela, Holland, India, Finland, Malta, Austria, Poland, Spain, Greece and China. Educational background varied widely within our cohort ranging from those who had attained university degrees to those who left school at 16.

7.1.3.2. Clinical characteristics

All groups were of comparable age, sex and years of education (see Table 7-2). There was a high frequency of vascular risk factors throughout, and there were more diabetics in the MCI group compared with the controls (see Table 7-3).

Table 7-2 Baseline characteristics of the three study groups

	CNTRL	MCI	SNCI
Number	33	21	35
Age	62.6 (8.7)	65.3 (8.0)	62.7 (9.3)
Sex M:F	15:18	13:8	15:20
Years Education	14.1 (2.7)	13.9 (2.8)	14.4 (2.7)

Means are given with the standard deviations in brackets. There was no significant difference seen in any of the variables above across the groups.

Table 7-3 Vascular risk factors

	CNTRL	MCI	SNCI
Systolic BP	144.5 (16.2)	146.5 (17.8)	137.4 (19.9)
Diastolic BP	87.2 (11.2)	84.4 (10.5)	82.4 (11.0)
IHD	12%	19%	3%
High cholesterol	33%	57%	40%
AF	0%	0%	0%
DM	0%+	19%+	9%
Past history TIA/CVA	0%	0%	0%
Treated hypertension	30%	43%	31%

+ There was a significant difference (p=0.02) in history of diabetes between the CNTRL and MCI group

Anticholinesterases

Three MCI subjects were on stable doses of anticholinesterases for treatment of memory impairment at the start of the study. Two MCI subjects were taking 10mg of Donepezil once a day. One MCI subject was maintained on 5mg once a day. No SNCI subjects had been prescribed anticholinesterases prior to the study.

ApoE analysis

ApoE genotyping was carried out on all individuals in the study. Sixty-seven percent of the MCI group, 37% of the SNCI group and 21% of the controls carried an ApoE4 allele. The allele frequency was significantly different between the MCI and SNCI

group (p=0.03) and MCI and controls (p=0.001). Five MCI, one SNCI and no controls were ApoE4 homozygous.

Clinical questionnaires

Both the clinical anxiety scale and geriatric depression scale indicated only mild levels of anxiety and depression in the groups with memory symptoms (see Table 7-4). There was a significant difference in CDR scores between the MCI and SNCI groups when the sum of boxes from the CDR was compared, but not in the overall rating. The MFQ findings are discussed in detail in section 7.5.

Table 7-4 Clinical questionnaire scoring at baseline

	MCI	SNCI	P-Value
Clinical Anxiety Scale (Max = 20)	1.67 (1.65)	2.69 (2.17)	0.07
Geriatric Depression Scale (Max =15)	1.14 (1.96)	1.17 (1.77)	0.82
Clinical Dementia Rating	0.45 (0.15)	0.33 (0.24)	0.056
Clinical Dementia Rating (sum of boxes)	1.71 (1.01)	0.54 (0.57)	<0.0001

7.2. Neuroimaging

7.2.1. Methods

7.2.1.1. Data collection

All subjects had MR imaging as previously detailed. All baseline MR scans were reviewed by a consultant neuroradiologist who was blinded to the clinical details of the subject. Poor scan quality due to movement artefact resulted in exclusion of one T1 weighted volumetric image (control) and five T2 weighted dual spin echo images (4

controls, 1 SNCI) from the analysis. Hippocampal volumes segmentation was carried out at a later stage (see chapter 10), leading to availability of 29 control, 35 SNCI and 20 MCI images.

7.2.1.2. Data analysis

Image processing was performed using the MIDAS software. Brain volumes for each scan were calculated directly from the MIDAS software tool, with correction for total intracranial volume (TIV). Ventricular volumes were also measured, as were WMH volumes. To compare groups, t-tests were used if data were normally distributed. Variances were compared between groups using F-tests and the form of the t-test adjusted accordingly. Where data were not normally distributed the Wilcoxon rank sum test was used.

7.2.2. Results

7.2.2.1. Visual assessment of MRI scans

In total nine MCI, three SNCI and one control subject were noted to have small hippocampi.

7.2.2.2. Quantitative assessment

Mean brain volume corrected for TIV, ventricular volume, hippocampal volumes and white matter hyperintensity (WMH) volumes are given in table 7-7. Graph 7:1 shows how the TIV corrected brain volumes were distributed across the different groups.

Table 7-5 Mean whole brain and ventricular volumes.

P-values are given for between group comparisons of means, standard deviations are in brackets, whole brain volumes are corrected for trans intracranial volume (TIV)

	CNTRL	MCI	SNCI	C v M	C v S	S v M
BrainVolume (ml)	1154.4 (62.6)	1115.9 (59.0)	1136.0 (60.9)	**0.03**	0.23	0.23
Ventricles (ml)	26 (22.8)	40.6 (25.5)	25.0 (14.8)	**0.04**	0.85	**0.01**
R Hippocampal volume (ml)	2.95 (0.5)	2.50 (0.6)	2.91 (0.4)	**0.002**	0.73	**0.002**
L Hippocampal volume (ml)	2.78 (0.3)	2.40 (0.6)	2.79 (0.5)	**0.006**	0.91	**0.004**
WMH* (ml)	1.59 (3.3)	0.71 (0.9)	2.1 (4.5)	0.66	0.48	0.21

*** White matter hyperintensities**

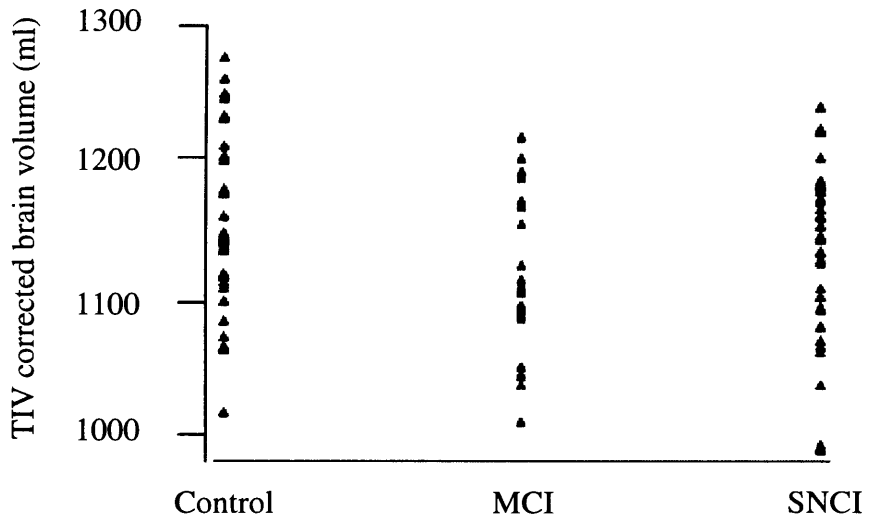


Figure 7-1 Distribution of TIV corrected brain volumes across the control, MCI and SNCI groups

7.3. Neuropsychology

7.3.1. Methods

7.3.1.1. Data collection

All subjects underwent a neuropsychological assessment as previously described. Individuals were assigned to either SNCI or MCI based on their performance on tests of memory. Where tests had a strong language component, analysis was carried out including and excluding those 11 subjects with English as a second language (Tables 7-5 and 7-6).

Where the whole cohort did not complete a test (see 6.3.2), the number of those who did is recorded beside the tests. Trails difference was a score calculated from the difference in performance on part A and part B of the TMT. This score gives an indication of executive functioning whilst correcting for motor speed (Drane et al. 2002).

7.3.1.2. Data analysis

All neuropsychological scores were converted to scaled or graded scores using published tables of normative values. Comparisons of neuropsychology scores between groups were made using regression models that were adjusted for age and education. If variables were normally distributed but with different variances in each group robust standard errors were reported. Where the variables were not normally distributed bias corrected bootstrap confidence intervals (1000 replications) were calculated and used to infer statistical significance.

7.3.2. Results

The baseline neuropsychology results for the cohort are shown in Table 7-5.

Table 7-6 Baseline neuropsychological performance across the groups

Mean scaled scores are given unless otherwise indicated. Standard deviation in brackets

Test	CNTRL	MCI	SNCI	C v M	C v S	S v M
MMSE*	29.79 (0.5)	27.95 (1.6)	29.49 (0.9)	**<0.001**	**<0.001**	0.11
NARTIQ* (31/21/26)	113.47 (10.9)	104.62 (17.7)	111.96 (13.2)	**0.031**	0.56	0.08
WasiVocab (31/21/26)	13.13 (2.3)	11.33 (3.4)	13.42 (2.4)	**0.016**	0.63	0.06
WASI Matrices	13.39 (2.5)	11.95 (2.8)	11.89 (2.5)	**0.012**	**0.009**	0.59
FSIQ* (31/21/26)	119.59 (12.8)	110.38 (14.2)	117.31 (12.2)	**0.004**	0.37	0.22
CVLT Immed. Recall	13.39 (1.9)	7.24 (3.4)	12.31 (2.7)	**<.001**	0.08	**<.001**
CVLT Delayed recall	14.27 (2.0)	7.00 (4.2)	12.46 (2.1)	**<.001**	**0.001**	**<.001**
CVLT Recognition†	13.48 (1.2)	7.05 (3.7)	13.00 (1.6)	**<.05**	>0.05	**<.05**
RMTW†	13.12 (1.6)	6.57 (2.4)	12.63 (2.3)	**<.05**	>0.05	**<.05**
RMTF†	11.64 (3.2)	6.67 (3.7)	12.77 (2.9)	**<.05**	>0.05	**<.05**
ROFCopy* (29/20/29)†	34.90 (1.4)	32.63 (5.1)	35.29 (1.0)	>0.05	>0.05	**<.05**
ROF Immediate Recall†	4.00 (1.5)	1.1 (1.5)	3.11 (1.7)	**<.05**	**<.05**	**<.05**
ROF Delayed Recall (29/19/29)†	3.93 (1.5)	0.5 (1.1)	2.90 (2.1)	**<.05**	**<.05**	**<.05**
GNT (31/21/26)	12.66 (3.1)	10.19 (3.2)	12.27 (3.6)	**0.01**	0.50	0.12
VOSP	9.30 (2.5)	8.29 (2.8)	9.00 (2.9)	0.14	0.56	0.6
TrailsA	10.25 (2.9)	8.87 (3.1)	9.31 (2.9)	0.1	0.2	0.6
TrailsB	11.42 (2.3)	8.63 (2.7)	9.7 (3.6)	**0.0002**	**0.02**	0.24
Trails difference (seconds)*	39.64 (21.3)	77.43 (51.4)	66.6 (53.9)	**0.004**	**0.003**	0.83

Where numbers are given in brackets in the 'Test' column, these reflect the actual numbers in each group (Control/MCI/SNCI) where analysis was undertaken, either because English was a second language, or because the test was not administered until after the study started (ROF).

***MMSE and trails difference performances were raw scores, the ROF was graded, and the FSIQ and NART were scored on an IQ scale**

The final three columns give the p-values obtained on group comparison e.g. C v M corresponds to control compared to MCI group.

† denotes neuropsychological tests analysed with bootstrapping and therefore with a corresponding p-value of greater or less than 0.05.

Table 7-7 Analyses of neuropsychological performance for the whole cohort

Including those without schooling in English to the age of 11.

Test	CNTRL	MCI	SNCI	C v M	C v S	S v M
NARTIQ	112.88 (11.2)	104.62 (17.7)	107.4 (14.8)	**0.035**	**0.028**	1.00
WASIVocab	13.12 (2.2)	11.33 (3.4)	12.74 (2.8)	**0.026**	0.31	0.26
FSIQ	119.21 (12.8)	110.38 (14.2)	114.09 (14.8)	**0.003**	**0.049**	0.74
GNT	12.51 (3.2)	10.19 (3.2)	10.69 (4.6)	**0.014**	**0.041**	0.90

Although individually the MCI group were only differentiated from the SNCI and control group based on performance on tests of memory, at a group level they also achieved lower scores on all indices of IQ, on tests of reasoning, naming and a test of visuoperception. The control group scored more highly than the SNCI group on the CVLT delayed recall, the ROF immediate and delayed recall, and on TMT part B, Trails difference and the matrices subset of the WASI.

Individual impairments

Although all individuals fulfilled criteria for MCI and SNCI as previously outlined, it was noted that throughout all three groups there were a number of individuals who would have been classified as impaired on the VOSP, EFT or the TMT using a cut-off of 1.5SD from the mean as for the memory tests. These included five controls impaired on one test; ten SNCI on one test, and two on two tests; and two MCI on one test, two on two tests and one on all three. None of these subjects complained of any symptoms other than memory impairment (in the MCI and SNCI). In view of these impairments these subjects were clinically reviewed individually at a multidisciplinary meeting and all were felt to have been correctly categorised as control, MCI or SNCI. Performance

on the GNT could not be assessed in this way due to the number of individuals who did not have English as a first language.

7.4. Discussion

The baseline analysis shows that the subject groups in this study are of comparable age, sex and education. In addition, the cohort has a similar and substantial number of risk factors for vascular disease despite exclusion of individuals with a history of or evidence on MRI of cerebrovascular disease. At least a third of our cohort had treated hypertension and a high cholesterol level, although the prevalence of high cholesterol in our group as a whole was lower than that of the general population of the UK, estimated at 48% (Hoare J et al. 2005). Despite these risk factors, the amount of WMH (representing vascular damage within the brain) remained low in our cohort, with no significant difference between groups in amount. WMH have been found to correlate with cognitive impairment in other studies (Petkov et al. 2004) and the lack of this relationship in this study may be a reflection of our exclusion criteria leading to a group relatively free of white matter disease.

There was a low level of affective symptoms across the MCI and SNCI groups. This finding is different to other population studies where symptoms of memory loss have been found to be strongly associated with increased levels of anxiety or depression (Jorm et al. 2001). The low depression and anxiety scores seen in our groups may reflect the fact that most subjects were referred by general practitioners, psychiatrists and neurologists. Those subjects who had obvious depression or anxiety-related memory symptoms were more likely to be treated for this or referred elsewhere, rather than recommended for this study.

Although all subjects fulfilled criteria for normal general cognition, had a CDR of 0.5 or less and were clinically judged to fall into the category of control, MCI, or SNCI, 25% of the total cohort scored at or beneath 1.5SD from the mean on normative values on one or more tests in our neuropsychological battery.

It is difficult to interpret the significance of these impairments across all three groups. The use of arbitrary cut-offs in a battery designed to be sensitive and stringent enough

to detect cognitive decline within a minimally impaired group may inevitably find a group of 'normal' individuals impaired. These scores may reflect the performance of individuals with below average IQs, who would routinely score close to the 1.5SD cut-off. Saxton et al (Saxton et al. 2004) found that over an eight-year follow-up 20% of their 'non demented' subjects with 'impaired' scores at baseline (1.5SD) did not progress to dementia, with impairments associated with both a decreased education and increased age. However in our cohort, those with impairments in non-memory domains were neither older nor less educated than the rest of the cohort.
Alternatively, our definition of 'impairment' may be too stringent. Other groups (Saxton et al. 2004;Storandt et al. 2006) have required low scores in at least two tests within a cognitive domain for an individual to be categorised as impaired. In our cohort only two subjects out of eighteen were impaired on both the VOSP and EFT, which are both tests of visuoperceptual ability. Although impairment on only one test of memory was used to categorize an individual as an amnestic MCI, it is of note that 80% of the MCI cohort was impaired on at least two.

It is indeed of interest that although all the MCI subjects recruited to this study fulfilled the Petersen criteria for amnestic MCI, that there were a number of subjects within the MCI group that could also have been classified as multidomain MCI, depending on the level of functioning chosen to represent impaired cognitive performance. For the purpose of clarity, and also for the reasons outlined above (arbitrary cut-offs in determining impairment, and limited number of non-memory tests used to determine impairment in non-memory domains), these subjects remained classified as amnestic MCI throughout the study. However, to address this overlap in definition between amnestic and non amnestic MCI, detailed analysis of how these non-memory impairments progressed or regressed during the two year follow up was carried out in chapter 9.

Our control group were (as far as possible) age and sex comparable relatives or spouses of the MCI or SNCI subjects in this study. In some ways this cohort may have been 'healthier' than a randomly selected group of volunteers from the general population, as they possessed a low number of vascular risk factors. Similarly to the MCI and SNCI, several (5) control subjects performed beneath the 1.5SD cut-off on one non-memory test. Using the 1.5SD cut off, in a normal population it would be expected that if performance on a test were normally distributed that 13.59% of the population would

have scores that fall beneath this cut off level. This percentage corresponds to 4.48 subjects in our study and is therefore roughly equal to the observed result. As such it was not thought likely that this group differed markedly from the rest of the population in terms of cognitive function.

Whether all these individuals are normal or in the early stages of a neurodegenerative disease will be determined during the course of this study. These findings do however highlight the difficulty in using arbitrary cut-offs on neuropsychological tests, and using performance on one cognitive test alone to determine function within a cognitive domain.

Although these groups had several similarities, there were also some marked differences. These included the number of risk factors for AD, cognitive functioning and baseline brain and ventricular volumes. In this next section the MCI and SNCI groups are taken in turn and their differences are discussed.

7.4.1. MCI

In keeping with the status of MCI as 'preAD', this group possessed more risk factors for AD than either the SNCI or the controls. There were an increased number of diabetics and carriers of the ApoE4 allele, and both cognitive performance and brain volumes were suggestive of preclinical Alzheimer's disease.

There were significantly more diabetics in the MCI cohort. Diabetes, along with hypertension and heart disease is a risk factor for development of AD and as such this difference between groups is expected. The frequency of diabetes and treated hypertension in our MCI group, was similar to other studies of amnestic MCI (Lopez et al. 2003). The effect of vascular risk factors on developing AD is thought to be accumulative (Luchsinger et al. 2005). The overall prevalence of an ApoE4 allele in this group was 62%. Other studies in amnestic MCI have found Apo4 allele frequency to range between 25-65% (Devanand et al. 2005;Fleisher et al. 2005;Lopez et al. 2003).

Neuroimaging analysis showed that brain and hippocampal volumes in the MCI group were substantially decreased compared with the controls and SNCI at study entry.

Atrophy of cerebral structures such as the medial temporal lobe and hippocampus are recognised as predictors of cognitive decline and our results are in keeping with these findings (see Chetelat et al 2003(Chetelat and Baron 2003) for review).

In a group possessing many risk factors for AD, it may seem incongruous that the majority of subjects were male whereas AD more commonly affects women. Studies of prevalence and incidence of amnestic MCI have yielded conflicting data regarding sex distribution. Some have found equal sex distribution (Fisk and Rockwood 2005) whilst others like our study have found males to be more commonly affected (Ganguli et al. 2004). This is at odds with the increased prevalence of AD in women, although it has been postulated that this sex ratio may in fact reflect differences in longevity of life and disease duration, or be an artefact due to poor age adjustment in studies (Baum 2005).

By definition, the MCI group were differentiated from the controls and SNCI by performance on memory tests. In addition, although each individual had memory impairment with normal general cognitive functioning at a group level, compared with controls, there were significant differences in IQ, naming, executive function and visual perceptual skills. This profile fits with the progression of impairment expected on progressing from MCI to AD(Lambon Ralph et al. 2003).

7.4.2. SNCI

Whereas the MCIs represented a group with multiple risk factors for the development of AD, the picture was less clear in the SNCIs. Although possessing risk factors intermediate in number to the MCI and controls (i.e., baseline brain volume, DM and high cholesterol) these differences failed to reach significance, perhaps due to study numbers. At 35% the frequency of ApoE4 allele was greater than the control group, which had a frequency comparable to the normal population at around 20% (Dufouil et al. 2005;Lopez et al. 2003). The frequency of the ApoE4 allele in the SNCI could perhaps represent heterogeneity in the group comprising some individuals likely to progress to AD and others that have symptoms of memory impairment related to personality, social circumstances or psychological symptoms.

Scores on tests of memory (delayed recall), reasoning and executive function, however, were significantly lower in the SNCI than the controls, whilst not reaching the levels of MCI performance. These differences could be explained by anxiety related to the demanding neuropsychological tests taking place. An alternative explanation would be that some individuals within this group were exhibiting a cognitive profile that would be consistent with the early stages of AD. Indeed the combination of poor performance on tests of delayed recall and abstract reasoning has been found to be predictive of later AD (Elias et al. 2000).

7.5. Memory Functioning Questionnaire

7.5.1. Introduction

Thus far we have investigated the cognitive functioning, risk factors for AD, and neuroimaging appearances of those complaining of memory loss, now we turn to their presenting complaint itself.

Memory complaints are a common reason for seeking medical advice. Assessment of such complaints involves taking a clinical history including type and duration of symptoms, asking an informant (close friend or spouse) for their opinion on this report and gathering an account of everyday functioning including whether memory aids are used. It is often unclear, however, what significance this information has in terms of predicting actual cognitive functioning and prognosis.

The aim of this chapter is to evaluate the nature and degree of memory complaints in our study cohort and examine their relationship to cognitive impairment and appearance of brain substructures. We also evaluated the relationship of other aspects of the clinical history including informant history, memory aid usage and duration of memory symptoms to cognitive impairment and brain appearance.

7.5.2. Methods

7.5.2.1. Data collection

At the baseline study visit all MCI and SNCI were given a 'Memory Functioning Questionnaire' (MFQ) and a clinician (HA) recorded the type and duration of their memory symptoms (see 6.3.1.3). The informants were also asked to complete this questionnaire as a record of their experience of their friend's memory performance. Administration of the same questionnaire to both informants and subjects allowed a direct comparison between informant and subjective memory ratings. All subjects had cognitive testing and neuroimaging as previously outlined with a senior neuroradiologist reporting all MRI scans (see 6.4.1).

7.5.2.2. Data analysis

Initial analysis examined whether four aspects of the clinical history could predict subsequent performance on memory tests and neuroimaging appearance. Further analysis was carried out to determine what combination of these components best predicted whether a patient would be impaired or not on tests of memory (CVLT or RMT) and therefore classified as MCI or SNCI.

Linear regression models were used to investigate associations between the total informant and subjective memory ratings, memory aid ratings and duration of memory symptoms and each neuropsychological z-score. Associations were adjusted for differences in education by including years of education as a four-level categorical covariate (<12, 12-13, 14-16 and 17+ years) in the regression models. Linear regression models relating these symptoms of memory impairment to whether or not the hippocampi were judged to be small clinically were adjusted for both age and education. Logistic regression models, using likelihood ratio tests to assess statistical significance, were used to assess associations between the clinical judgment that hippocampi were small and the outcome of memory tests. Again, associations were adjusted for differences in education by including years of education as a four-level categorical covariate (<12, 12-13, 14-16 and 17+ years) in the models. In all of these analyses no Bonferroni type corrections for multiple comparisons were made since each of these associations was judged to be of independent scientific interest.

Forward stepwise logistic regression, using likelihood ratio tests to assess statistical significance, was employed to assess which variables independently predicted whether subjects fell into the MCI or SNCI group and which were judged to have small hippocampi. All statistical analyses were carried out using STATA statistical software version 8.2(1984).

7.5.3. Results

7.5.3.1. Subjective symptoms

All subjects were able to provide the name of an informant whom they saw regularly and could answer questions regarding their memory impairment. The majority were spouses, relatives or close friends. A minority were either known to the patient through their employment or were a health professional who had known them for a number of years.

The most common symptom of memory impairment listed was difficulty in remembering names. The distribution of symptoms is shown in Table 7-8.

Table 7-8 Subjective and informant rated memory problems

Median and interquartile ranges are given

	Patient rating		Informant Rating	
Symptom of forgetting	Median	*IQ range (25%-75%)	Median	IQ range (25%-75%)
Names	4	3-4	4	3-5
Faces	4	3.5-5	5	4-6
Appointments	5	4-6	4	3-6
Where things have been put	4	3-5	4	2.5-5.5
Chores	5	4-6	6	4-7
Directions to places	4	3-6	5	3-6.5
Telephone numbers used frequently	5	4-6	5	4-6.5
What you have been told by someone	4	3-4.5	3	2.5-5
Keeping up with correspondence	5	3.5-6	5	3.5-7
Birthdays	5	3-6	5	4-7
Words	4	3-5	6	4-7
Shopping	4	3-5.5	4	3.5-6
Beginning to do something and then forgetting what you were doing	4	3-6	5	4-6
Losing the thread of thought in conversation	4	3-5	4	3-6
What you had told someone	4	3-5	4	2-5
Total memory rating	64.5	56.5-71.5	72.5	56.5-81.5

Memory ratings were based on a scale of one to seven with a score of one reflecting constant difficulty with a particular task, and a score of seven no difficulty.

*** IQ range = interquartile range**

Neither age, gender, years of education, anxiety, nor depression ratings were significantly related to the total amount of memory complaints for each individual. The only significant association with cognitive function was a positive correlation between performance on Part B of the Trail Making Test and subjective memory complaints $p=0.015$, $r^2=0.11$.

In total 12 of the group were noted to have small hippocampi on volumetric MR imaging. There was no evidence of a relationship between subjective memory loss and hippocampal appearance.

7.5.3.2. Informant impression of memory impairment

The most common problem perceived by the informant was that the subject would forget information that they had previously been told. There was evidence that the informant rating was associated with the subject's performance on tests of memory (CVLT immediate recall p=0.009, CVLT delayed recall p=0.01, CVLT delayed recognition p<0.001, RMT words p=0.001 and RMT faces p=0.034). There was also evidence of an association between informant rating and clinical impression of hippocampal size, which was maintained on controlling for age (p=0.003).

7.5.3.3. Duration of memory symptoms

Duration of memory symptoms ranged from one to 20 years with a mean of 5.1 (SD 4.3 years). Where an individual had a long history of memory symptoms, they performed better on the RMT for faces (0.017). There was no evidence of a relationship between duration of memory symptoms and neuroimaging results.

7.5.3.4. Use of memory aids

Subjects and informants were additionally asked about the use of memory aids, such as diaries and reminders lists. The use of memory aids was significantly associated with a lower age (p= 0.005) but not with education. There was a positive relationship between use of memory aids and performance on the CVLT, with those using memory aids attaining higher scores (CVLT immediate recall p=0.036, CVLT delayed recall p=0.022). There was a relationship between a decreased use of memory aids and small hippocampi (p=0.012) although this was no longer statistically significant (p=0.067) on controlling for age.

7.5.3.5. Group discrimination

Informant ratings, use of memory aids and duration of memory complaints were assessed for their ability to discriminate between the (a) MCI and SNCI groups (i.e. those with and without memory impairment) and (b) whether an individual was judged clinically to have small hippocampi on MRI. In both cases the informant rating was the most significant variable for group discrimination (p=0.0002 and p=0.007 respectively). The addition of memory aid to informant rating further improved discrimination in both cases (p=0.02 and 0.006 respectively). Table 7-9 shows that after mutual adjustment a 10-unit decrease in the informant rating score multiplied the odds of being in the MCI group by 2.2 whilst a 10-unit increase in the use of memory aids score multiplied these odds by 2.4. Similarly sized associations were seen for the associations between these variables and small hippocampi. The addition of the duration of memory symptoms did not further improve discrimination in either case.

Table 7-9 Informant ratings, memory aids and cognitive impairment

Crude and adjusted odds ratio relating the odds of being in the MCI group (vs. SNCI) to 10-unit changes in informant rating and use of memory aids scores.

	Odds ratio (95% confidence interval)	
	Crude	Adjusted
Informant Rating (10 unit decrease)	2.0 (1.3, 3.1)	2.2 (1.4, 3.5)
Use of Memory Aids (10 unit increase)	1.9 (1.0, 3.5)	2.4 (1.1, 5.1)

Table 7-10 Informant ratings, memory aids and hippocampal size

Crude and adjusted odds ratio relating the odds of having small hippocampi to 10-unit changes in informant rating and use of memory aids scores.

	Odds ratio (95% confidence interval)	
	Crude	Adjusted
Informant Rating (10 unit decrease)	1.7 (1.1, 2.6)	1.9 (1.2, 3.2)
Use of Memory Aids (10 unit increase)	2.6 (1.2, 6.0)	3.1 (1.3, 7.5)

7.5.4. Discussion

Analysis of the memory functioning questionnaire shows that in our cohort (1) informant rating, use of memory aids and duration of memory complaints but not subjective ratings of memory were predictive of memory test performance, (2) informant ratings were also associated with hippocampal size on MRI and (3) when informant rating, duration of memory complaints and use of memory aids were compared, informant rating was the most statistically significant independent predictor of both objective memory impairment and small hippocampi.

The most common symptom patients complained of was forgetting names, which is in accordance with population studies of normal ageing. Unlike other studies, however, we did not find age, education or gender to be related to subjective memory ratings, and our group as a whole obtained low scores on scales of depression and anxiety (Zelinski and Gilewski 2004). This may reflect the difference between a memory clinic cohort and population study, with subjects sourced from clinical referrals excluding those with significant psychiatric symptoms. This may also reflect the difference between those seeking help for memory problems as opposed to those being approached for involvement in a study.

Informants most commonly noticed that their relative or friend would forget something that they had been told. This may be most easily noticed by informants as a consequence of day-to-day interactions or alternatively may be the manifestation of a decline in the patient's verbal episodic memory, a domain affected early in AD.
The correlation of informant memory rating to subjects' performance on memory tests is consistent with previous work (Kemp et al. 2002;Ready et al. 2004). Some studies (Tierney et al. 2003) but not all (Knafelc et al. 2003) have found that adding informant rating to brief cognitive tests can increase accuracy of diagnosis of cognitive impairment. Still other studies have found informant ratings to be more sensitive and specific for cognitive impairment than brief cognitive tests alone (Jorm 1997). In our study, however, the informant rating was also associated with neuroimaging findings. Hippocampal atrophy is among the first and most consistent of the changes seen on neuroimaging in AD compared with controls (de Leon MJ et al. 1989);(Jack, Jr. et al. 1992). The relationship between memory symptoms and hippocampal size has not been

widely investigated. A correlation between informant rating of memory and decreased hippocampal size has been reported in one study (Farias et al. 2004) although this was explained by the effects of age on hippocampal size. In our study the relationship between hippocampal size and informant rating was present whilst controlling for age, suggesting that changes in the hippocampi were related to the disease process (potentially AD) not natural aging. Small study numbers have precluded evaluation of the characteristics of informants that make them reliable. A substantial literature on this question does currently exist, and educational history, quality of relationship, informant depression, perception of normal ageing and frequency of seeing the subject have all been found to affect the reliability of a rating (Cacchione et al. 2003;Jorm 2003).

Decreased use of memory aids was associated with poorer performance on tests of memory. Those of a younger age group used them more frequently. This may reflect difficulty adopting new memory strategies with ageing or increased memory impairment in some subjects, or perhaps memory aids were thought unnecessary by more impaired subjects because of limited insight (a feature of AD) into memory problems (Ott et al. 1996). When fewer coping strategies were used by individuals with impaired memory, memory problems may have been more obvious to informants.

Extrapolation of these results is limited by their cross-sectional nature. Although directly applicable to a clinical setting, most population studies that have demonstrated a relationship between subjective symptoms and cognitive impairment have been longitudinal (Geerlings et al. 1999;Schofield et al. 1997). Although subjective symptoms of memory loss did not predict current cognitive functioning at this stage we have not investigated whether these symptoms predict future cognitive decline. This will be the subject of the longitudinal follow-up section of this thesis.

7.6. Conclusions and summary of baseline results

In summary we describe a clinical cohort of individuals with varying degrees of memory impairment, from subjective symptoms alone to those with symptoms and memory impairment on neuropsychological testing. Along with a control cohort these groups have been well characterised and have shown differences at the group level in terms of vascular risk factors, ApoE4 genotype, neuropsychology and neuroimaging.

The amnestic MCI represent a group with risk factors for AD and a cognitive profile and neuroimaging findings consistent with early AD. The SNCI group most likely represent a heterogeneous group with some individuals in a 'pre MCI' stage and others that have symptoms of memory impairment related to personality, social circumstances or psychological symptoms and are therefore 'worried well'.

The results from the MFQ underline the importance of taking a thorough clinical history from individuals seeking medical advice regarding cognitive impairment. Information including an informant history, duration of memory symptoms and memory aid usage is valuable when relating symptoms of memory impairment to cognitive functioning. The informant rating of memory symptoms was most strongly predictive of neuropsychological performance and hippocampal size.

Correct identification of the individuals from this group who are in the 'preMCI' stage requires longitudinal follow-up with serial neuropsychological evaluation and neuroimaging. This is illustrated in the next chapter where such longitudinal follow-up detected the subtle changes associated with early AD in a 'PreMCI' individual which were not detectable on cross sectional assessment. Whether this finding will be mirrored in the longitudinal follow up of our cohort is the question and focus of the second part of this thesis.

8. Knight's move thinking? Mild cognitive impairment in a chess player

A case report

8.1. Introduction

It is often difficult for clinicians to identify which patients with memory complaints will go on to develop measurable memory deficits and progress to AD. This may be particularly relevant to high functioning individuals, where due to greater cognitive reserve absolute clinical deficit may not accurately reflect the underlying disease process. Generally it is only when a subject presents with memory deficits sufficient to impinge upon their daily functioning that a diagnosis of dementia can be made (American Psychiatric Association 1994) and therapy considered.

In this case report we describe a patient who presented with early symptoms of memory impairment, and subsequently declined to fulfil criteria for MCI. During the clinical transition from MCI to early AD, the subject died of other causes, permitting a definitive histological diagnosis of sporadic Alzheimer's disease to be made.

The subject was investigated and monitored throughout the disease process with sequential neuroimaging and neuropsychological evaluation, allowing assessment of the potential of these investigative tools to detect the onset of cognitive decline and monitor its progression.

8.2. Methods and materials

8.2.1. Neuropsychology

Neuropsychology was performed at four time points (See Table 8-1). A standardised battery was performed, including the National Adult Reading Test (NART) (Nelson and Willison 1991), the verbal and performance sub-scales of the Wechsler Adult Intelligence Score-Revised (WAIS)(Wechsler 1981), the Recognition Memory Test for words and faces (RMTw and RMTf)(Warrington 1984), paired associates learning test (PALT)(Warrington 1996), the Graded Naming Test (GNT)(McKenna and Warrington 1983), the Oldfield picture naming test (Oldfield and Wingfield 1965), two subsets from the VOSP battery (Warrington and James 1991), word fluency and cognitive estimates (Shallice and Evans 1978).

8.2.2. Magnetic resonance imaging

T1-weighted volumetric MR scans were acquired at five points, over a 36-month interval on the same 1.5-T GE Signa Unit (General Electric, Milwaukee, WI) using a spoiled gradient-echo technique (256 × 192 matrix, FOV 20 × 20 cm, TE 4.2–14/ INV 150/ NEX 1/ FLIP 20°) giving 124 contiguous 1.5-mm thick slices. T2-weighted and proton-density scans were acquired at each time point. An experienced neuroradiologist reported all MR scans. Image processing was carried out using the MIDAS software

tool (Freeborough et al. 1997). A previously described nine-degrees-of freedom rigid body registration (Freeborough et al. 1996) was used to match serial scans accurately to each other. The Brain boundary shift integral (BBSI)(Freeborough and Fox 1997) was used to quantify whole brain loss. Semi automated techniques, using intensity thresholding were applied to delineate regions of interest on registered scans and allow calculation of hippocampi and ventricle volumes at each timepoint.

8.3. Case history

A 73-year old right-handed retired academic presented to the Cognitive Disorders clinic at the National Hospital for Neurology and Neurosurgery in December 1998, reporting a two-year history of decline in his ability to play chess. He complained that whilst previously he could plan his game seven moves in advance, he could now only plan three or four. He had only noticed this change gradually with no suggestion of a stepwise decline in his abilities. His wife felt that he might be slower at picking up the subject of conversations and was becoming slightly more repetitive in his remarks; however, it was generally felt by the family that there were no significant cognitive impairments and that he alone was convinced that he was suffering from progressive memory loss. He continued to do the finances at home, and there was no change in personality, language, writing or praxis.

Medical history was unremarkable apart from a prostatectomy for bladder outflow obstruction (with benign histology). He was a non-smoker and there was no history of diabetes mellitus, hypertension or ischaemic heart disease. Information on cognitive impairment in other family members was not available.
General examination was unremarkable. He scored 27 out of 30 on the mini-mental state examination (MMSE)(Folstein et al. 1975). Investigations at that time revealed a normal chest x-ray and ECG; routine blood tests including thyroid function tests, autoimmune profile and vitamin B12 levels were normal apart from a raised cholesterol level at 6.9 mmol/L. The EEG showed a mild non-specific disturbance of cerebral activity in the left temporal region, with preserved alpha rhythm and no epileptiform activity. At the first assessment, the neuropsychological investigation was essentially within normal limits with only two exceptions, naming and verbal short-term memory. This average score coupled with a few circumlocution errors was taken to indicate mild

nominal difficulties in the context of his superior expressive and reading vocabulary even making allowance for German being his first language. His forward digit span was only five, which was also noticeable in the context of his otherwise high average/superior cognitive performance. Initial MRI scanning revealed generalised cerebral atrophy thought to be in keeping with normal ageing, although the hippocampal volumes were at the lower end of normal. White matter change compatible with mild vascular disease was noted as well as a small peripheral haemorrhage in the right parietal region. Whilst not reaching criteria for MCI (Petersen et al. 1999), the assessing clinician felt that the patient's history was suggestive of very early Alzheimer's disease.

Table 8-1 Serial cognitive assessment scores

Date	**7.12.98**	**26.7.99**	**4.5.01**	**23.4.02**
VIQ	117	128	118	127
PIQ	126	122	128	123
RMTw	47/50 (75-90%)	40/50 (25%)	40/50 (25%)	34/50 (<5%)
RMTf	43/50 (50-75%)	39/50 (25%)	35/50 (5%)	34/50 (<5%)
PALT T1	17/24 (75%)	14/24 (50-75%)	4/24 (5%)	8/24 (10-25%)
PALT T2	21/24 (50-75%)	18/24 (50%)	12/24 (10-25%)	12/24 (10-25%)
GNT	20/30 (25-50%)	18/30 (25%)	15/30 (10%)	13/30 (5%)
Oldfield	28/30	28/30	26/30	25/30
Object Decision	18/20	15/20	15/20	15/20
Incomplete letters	19/20		19/20	19/20
Word fluency	31 (S)	22 (S)	23 (S)	26 (S)
Cognitive estimates	reasonable	reasonable	reasonable	reasonable
Digit span	5	5	4	4

VIQ = Verbal Intelligence Quotient, PIQ = Performance Intelligence Quotient, RMTw = Recognition Memory Test for Words, RMTf = Recognition Memory Test for Faces, PAL T1 and PAL T2 = Paired Associate Learning Test trial 1 and trial 2, GNT = The Graded Naming Test (Percentiles in parentheses).

The patient was reviewed three times over the following year. During this period, neither he nor his wife reported significant progression of symptoms, although when playing chess he now reported a tendency to lose the pattern of play in addition to the difficulty in planning moves. The second MMSE 6 months after presentation was 28 out of 30. However, repeat neuropsychology at the same time revealed mild decline in both verbal and visual memory, as well as tests of perception and word retrieval (Table 8-1). A few semantic errors were noted (e.g.: trampoline for trapeze). Repeat MRI in November of 1999 was again reported as showing mild generalised atrophy within normal limits for his age. Registration of this scan to the initial MRI carried out 9 months earlier, however, demonstrated ventricular enlargement and hippocampal and whole brain atrophy, in excess of that seen in normal ageing.

He was next seen in February 2001 at which time he reported continued difficulty remembering day-to-day events and names. Although still reading historical books, he complained that this took longer than before and he had essentially stopped playing chess. Whilst still managing the home finances, he found this more difficult mainly due to problems with calculation. He continued to drive competently and was never disorientated in familiar surroundings. The MMSE was now 25 out of 30. His third neuropsychological assessment revealed a further decline in his verbal and visual memory function. For the first time he obtained scores at 5^{th} percentile on the visual recognition memory test and on the first trial of the paired associates learning test. With impaired scores, more than 1.5 standard deviations from the mean (Petersen et al. 1999), he now fulfilled diagnostic criteria for MCI. A further decline was also observed in his nominal functions. An EEG carried out at this time demonstrated occasional paroxysmal theta activity over the left fronto-temporal region but well preserved alpha rhythm.

In October 2001, his wife reported a slow but definite deterioration in his memory. She had taken over running of the home finances and the family had noticed that he had become increasingly repetitive in questioning. In July 2002 the patient reported that as well as his memory slowly worsening, he was less comfortable in social situations,

forgetting his colleagues' names and details of what he had recently read. He now reported getting lost in unfamiliar environments. He was still, however, enjoying his daily activities of shopping, cooking and chess, and had learnt how to use a computer.

The neuropsychological assessment at that time showed global severe memory and nominal impairment, the majority of his errors on the naming task were semantic and circumlocution. Interestingly his performance remained in the superior range on tests of general intelligence throughout the four assessments. MRI scans carried out in 1999, 2001and 2002 were compared using image registration, and showed pathological increase in ventricular size. A pathological decrease in hippocampal volume was seen comparing the baseline scan to those acquired in both 2001 and 2002 (Figures 8-2 and 8-4). The neuroimaging features were thought to be compatible with a diagnosis of Alzheimer's disease. In the light of reports of his high level of daily functioning (through correspondence and at consultations, from both the patient and his family), clinically the diagnosis was felt to fall between MCI and AD. The patient was offered treatment with a cholinesterase inhibitor, which he declined.

Shortly after the fourth assessment the patient died of an unrelated cause and a post-mortem examination was performed.

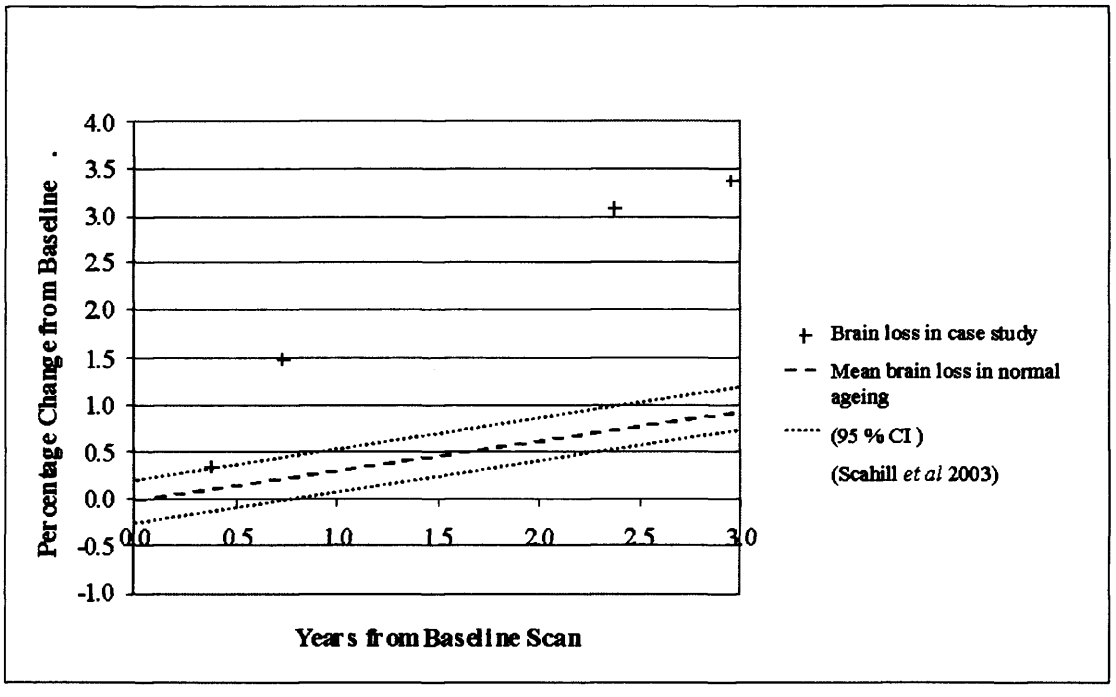


Figure 8-1 Percentage change in brain volume over a three year period.

The 95% confidence intervals are based on standard errors

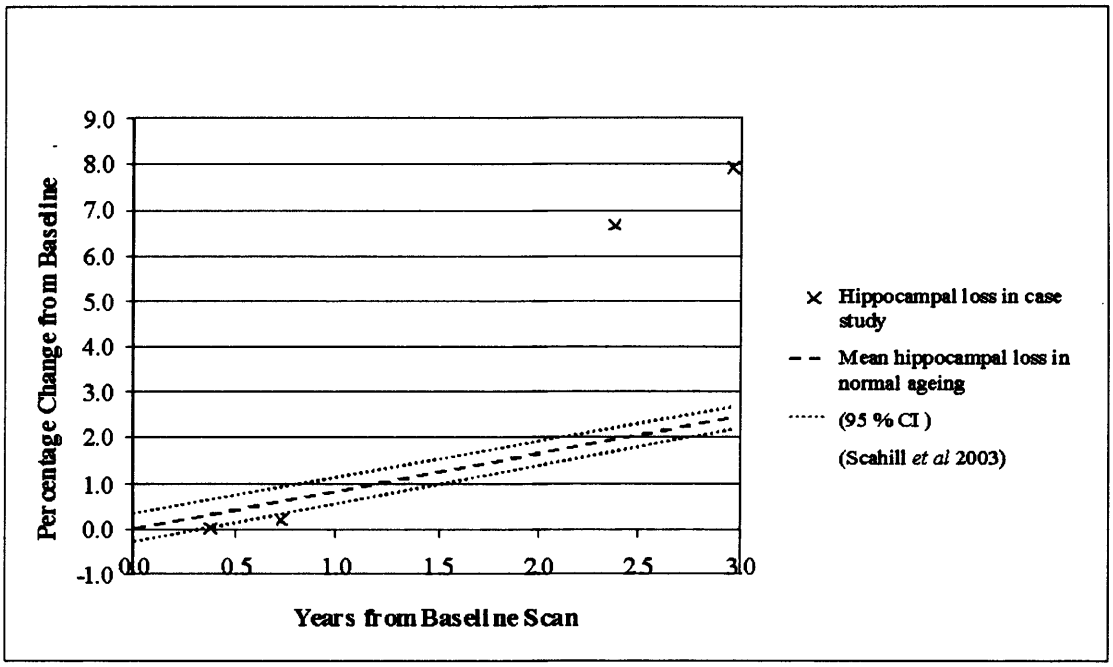


Figure 8-2 Percentage change in total hippocampal (left plus right) volume over a three year period

The 95% confidence intervals are based on standard errors

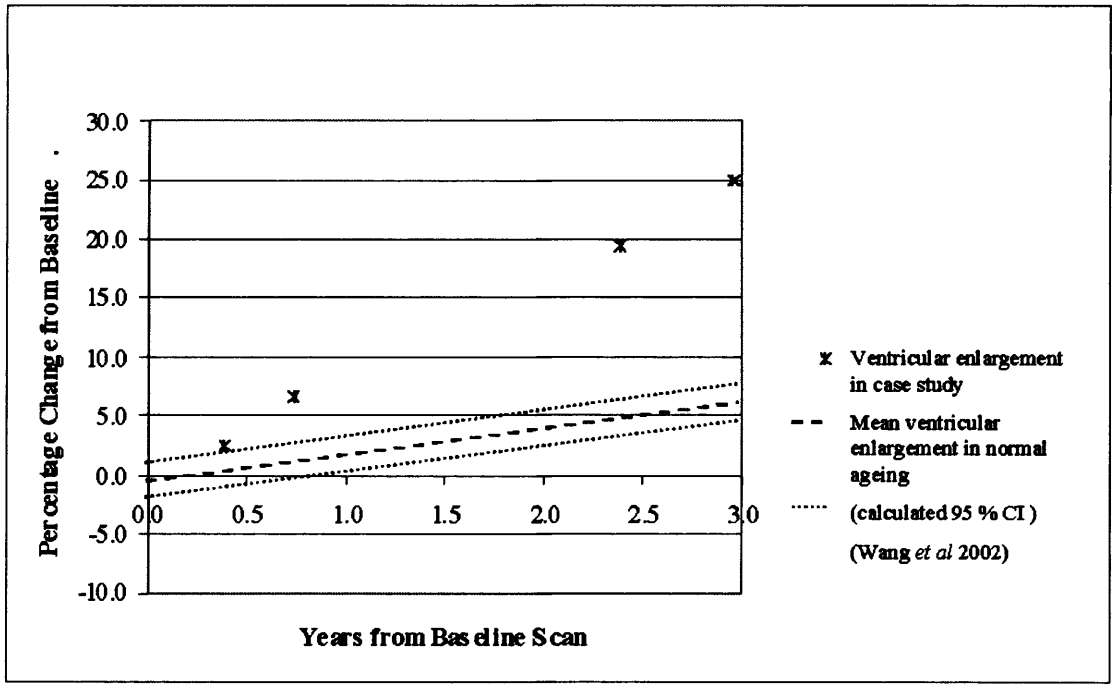


Figure 8-3 Percentage change in ventricular volume over a three year period

The 95% confidence intervals are based on standard errors

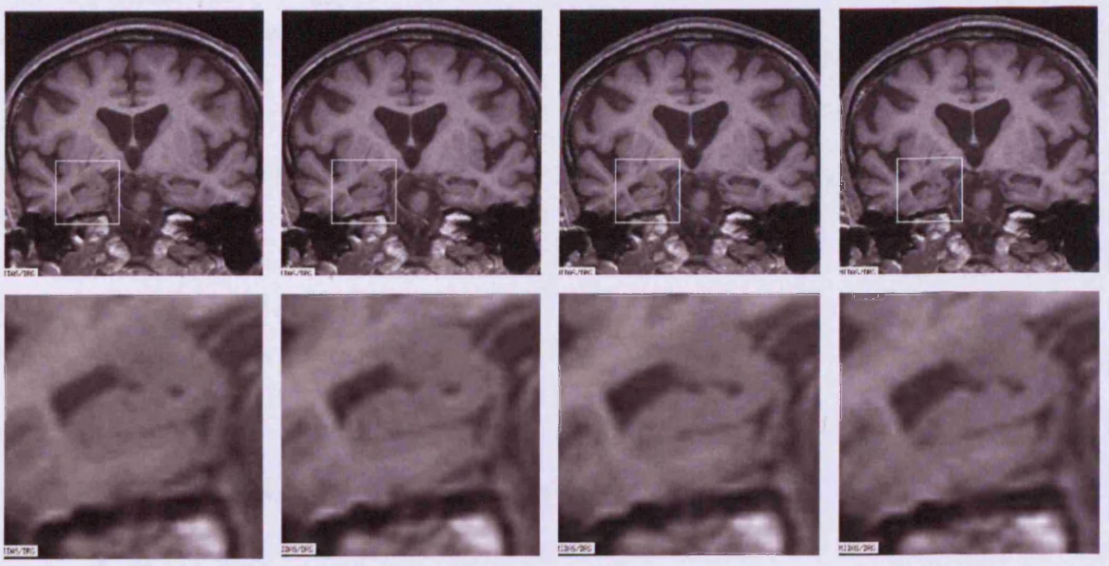


Figure 8-4 MRI showing coronal sections of the brain at baseline, nine months, two and three years (from left to right)

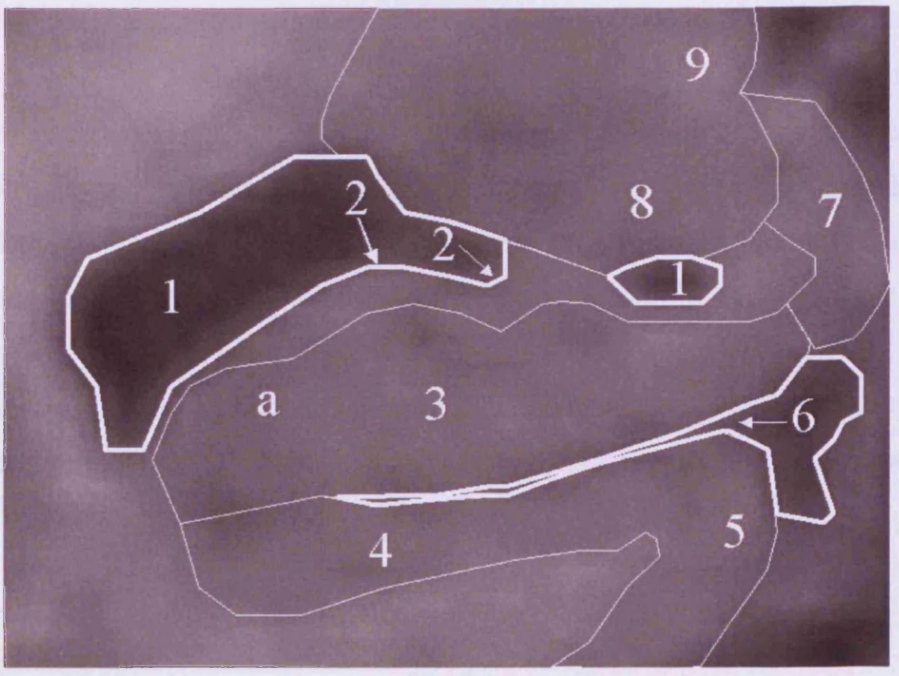


Figure 8-5 Schematic overlay showing the hippocampus and surrounding structures

key for drawings

1. **temporal horn of lateral ventricle**
2. **internal digitations**
3. **cornu ammonis a CA1**
4. **subiculum**
5. **parahippocampal gyrus**
6. **uncal sulcus**
7. **subiculum in uncinate gyrus**
8. **accessory basal nucleus of amygdala**
9. **cortical nucleus of amygdala**

8.4. Pathological examination

At post mortem the brain weighed 1318 grams. The right half of the brain was fixed in 10% formalin and examined neuropathologically while the left half was frozen and stored at -80°C. Neuropathological examination showed that there was minimal enlargement of the sulci of the right frontal lobe, but no other evidence of cortical atrophy. The temporal horn of the right lateral ventricle was moderately enlarged due to reduction in size of the posterior hippocampus. The main basal arteries showed mild atheroma. There was mild pallor of the locus coeruleus. Histological examination revealed frequent Aβ-positive neuritic plaques in the temporal neocortex, which were moderate in number in the frontal and parietal cortices. The severity and extent of the neurofibrillary tangle pathology was such that it corresponded to Braak and Braak stage VI. In addition there was evidence of severe cerebral amyloid angiopathy and Lewy body pathology in brainstem and limbic structures.

The diagnosis was of Alzheimer's disease (CERAD definite and NIA-Regan Institute high likelihood) with severe cerebral amyloid angiopathy and evidence of transitional Lewy body disease.

8.5. Discussion

This case demonstrates the limitations of currently available clinical investigation in the diagnosis of individuals with very early Alzheimer's disease. This is particularly relevant in high functioning individuals where, due to high cognitive reserve, the

absolute clinical deficit may not be proportional to the cerebral changes found on histopathology.

When first assessed, this gentleman who presented with a 2-year history of memory impairment had a neuropsychological assessment within normal limits for age and education, the only exception being a weak performance on nominal and verbal short-term memory tasks. MCI was diagnosed 2 years later after he had developed sufficient impairment on the visual version of the Recognition Memory Test and on one of the trials of the Paired Associate Learning Test to fulfil diagnostic criteria (Petersen et al. 1999). At his final assessment, it was unclear whether he met the criteria for probable Alzheimer's disease. Although there were documented impairments in recognition memory and nominal functions, these were at odds with reports of his daily functioning from his wife who maintained that at that time he had "excellent mental awareness". These results highlight the potential difficulty in detecting and following subtle memory deficits in high functioning individuals at the onset of a dementing process. Where MR images were individually reported as demonstrating changes within normal limits for ageing, registration of serial MR images suggested that increased cerebral atrophy characteristic of AD was occurring as early as 1999. Similarly the change seen on serial neuropsychological assessments better demonstrated and was more representative of the disease process than single assessments.

One of the difficulties in assessing cognitive complaints may be the qualitative rather than quantitative nature of the reported symptoms, such as misplacing objects or forgetting dates. Without an accurate knowledge of the premorbid state it is difficult to gauge whether the severity of symptoms has changed. In this case, the symptoms were quantifiable, as the subject described a change in his ability to plan from 7 moves ahead to only 4 in a game of chess.

Memory complaints are usually the first symptoms of Alzheimer's disease and occur before cognitive deficits can be demonstrated on tests (Fox et al. 1998). In this case the subject had subjective memory impairment two years prior to presentation. In longitudinal studies of subjects at risk of familial AD the most common symptoms declared by individuals who subsequently developed AD were very mild episodic memory problems (Fox et al. 1998). In this series the subject, spouse or close family

member typically noticed these problems 6 months prior to the first measurable cognitive deficits.
Population studies have also indicated that memory complaints are of importance particularly in highly educated elderly individuals, and should be taken seriously due to the ceiling effect of short cognitive screening tests (Jonker et al. 2000).

Many population studies have emphasized the importance of an informant history (i.e., from a spouse or relative) in the evaluation of memory complaints, particularly when investigating symptoms of memory loss as predictors of cognitive impairment (Jorm 2003;McGlone et al. 1990). The informant's impression of their relative's memory is important as it is likely to be more objective and less influenced by a patient's anxiety or depression. However, the drawback of relying too heavily upon this information is illustrated in this case, as well into the course of the disease his family felt that he had no perceivable memory deficits (letter written by the subject's wife prior to his third consultation in 1999).

Although initial MRI scans showed atrophy within the range for normal ageing, registration of the MR images from 1999 showed definite increased atrophy (Figure 8-4). These findings are in keeping with previous reports, demonstrating that both global and medial temporal lobe atrophy occurs years prior to diagnostic criteria being met (Jack et al. 2000;Rusinek et al. 2003;Schott et al. 2003). Repeat neuropsychological assessment revealed mild further decline in nominal and memory functions but certainly the advanced Alzheimer's pathology seen at post-mortem would not have been predicted in an individual with a clinical history of only mild decline in functioning, whose verbal and performance IQs were both still above 120. By contrast, the MR images compared over the same period revealed clear ventricular enlargement and medial temporal lobe atrophy (Figures 8-1 – 8-4) more typical of moderate to severely advanced Alzheimer's disease.

Whilst MCI is a useful concept, alerting both physicians and patients alike to the fact that there is a transitional stage between normal ageing and development of dementia, this case illustrates some of the problems still associated with the current diagnostic criteria for MCI. Criteria requiring memory to be impaired 1.5 standard deviations below the mean (Petersen et al. 1999) clearly require a greater decline of cognitive

function in high functioning individuals than in those performing at an average, or sub-average premorbid level.

When disease modifying treatments become available, it will become increasingly important to develop strategies for the early detection and diagnosis of AD (and its pathological correlates), to allow treatment to be introduced at a time when the patient can still benefit and pathology is not as advanced as it was in this case.

It is interesting to note that a percentage of cognitively normal elderly patients coming to post mortem are found to have a degree of AD pathology; this is in general to a lesser extent than that found in the current case (Knopman et al. 2003). These authors suggest that AD pathology appears to exert no dramatic influence on cognition until a certain threshold is reached. In this case report it seems likely that the severe AD pathology was responsible for the progressive cognitive deficits and imaging changes demonstrated. A consistent feature of Alzheimer's disease (even at its very early stages) is progression, and in the absence of an identifiable mutation as found in familial Alzheimer's disease, cognitive impairment is better demonstrated on serial assessments than on single measurement. An approach to detecting AD at an early stage might incorporate atrophy derived from serial volumetric MR imaging, alongside clinical and neuropsychological testing to detect subtle progressive cognitive impairment in high functioning individuals even if the cut off of 1.5 SD below the mean required by MCI criteria has not been reached.

9. Clinical outcome

9.1. Defining outcome

The end point of this prospective longitudinal study was the cognitive status of patients and controls at the second follow up visit. Clinical diagnosis and the change in score in the sum of boxes from the Clinical Dementia Rating (CDR) were used as outcomes.

9.1.1. Outcome 1 - Clinical diagnosis

Change in neuropsychological performance over two years and senior clinician review were combined to give a clinical diagnosis at 2 years. This was achieved through review of the neuropsychological performances of all subjects over two years, with detailed examination by a consultant neuropsychologist (EKW) where an individual showed impairment in performance on any test (defined as 1.5 standard deviations below age corrected normative values, for tests of memory or WASI matrices and $<5^{th}$ percentile for all other tests). If neuropsychological review revealed any decline in cognition over the two-year study period, that subject was reviewed by a consultant neurologist (NCF) who had not had any clinical involvement in the study. NCF had access to clinical notes and neuropsychological data, but was blinded to the results of their neuroimaging and clinical dementia rating. A diagnosis was given of either normal, MCI, AD or another neurodegenerative disease according to the criteria below. These outcome measures are similar to those recommended by Petersen et al 2006 (Petersen 2006).

Table 9-1 Clinical outcome criteria for MCI and AD used in this study

Petersen criteria for MCI	NINCDS-ADRDA criteria for the clinical diagnosis of probable Alzheimer's disease (Appendix 2)

• Memory complaint • impaired memory function for age and education (defined as scores > 1.5SDs below age appropriate mean), • preserved general cognitive function • intact activities of daily living • not demented	• dementia established by clinical examination and documented by the Mini-Mental Test; Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests; • deficits in two or more areas of cognition; • progressive worsening of memory and other cognitive functions; • no disturbance of consciousness; • onset between ages 40 and 90, most often after age 65; and • absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition

9.1.2. Outcome 2 - Sum of boxes at two years

The CDR is a clinically based measure with 6 categories used to rate dementia severity, directly linked to validated diagnostic criteria for AD. It has been found to have high inter rater reliability for both physicians and non physicians (Morris 1993). An expanded and more quantitative version of the scale can be achieved by summing their ratings in each of the 6 categories to provide the sum of boxes (Berg et al. 1988). An increase in score corresponds to decreasing functioning.

The CDR has been used as an outcome measure by epidemiological and clinical studies (Blacker et al. 2007;Galvin et al. 2005;Silveri et al. 2007;Storandt et al. 2006) and clinical trials (Rogers et al. 1998). Within these settings it has been found to be reproducible and a robust tool for assessing patients (Schafer et al. 2004). The CDR combines patient, informant and clinician opinion whilst remaining separated from

neuropsychological and neuroimaging assessment, and as such had been thought to confer a degree of objectivity (Petersen 2004).

9.1.3. Statistical analysis

Comparisons between outcomes and variables such as age, education, duration of memory symptoms, informant and subjective memory ratings and use of memory aids were made using t-tests (for outcome 1) and simple regression analysis with robust standard errors (for outcome 2 comparisons). Fisher's exact test was used to assess differences in clinical outcome between the control and SNCI groups.

9.2. Results

9.2.1. Subject retention

Subject retention over the two-year period of follow up was 100 per cent. Three controls were lost from the study over the first year, due to death (ischaemic heart disease), terminal illness, and a change in geographical location precluding further study involvement.

9.2.2. Clinical diagnosis

The results are shown in Table 9-2. One MCI subject declined neuropsychological testing at 2 years, and was excluded from this table, together with any analysis involving clinical diagnosis. Table 9-3 shows how the neuropsychological performance of the three groups changed over the 2 years of follow up.

Table 9-2 Clinical outcome in the pre MCI cohort

	No Clinical Progression	Clinical Progression	Conversion rate (%/y)
SNCI	31	3 – MCI, 1- AD	6.45
MCI	12-stable 2- SNCI	6 – AD	15

Table 9-3 Change in neuropsychological performance over two years in the pre MCI cohort

The table shows the number of individuals in each group who either improved their overall neuropsychological performance, maintained impairment in the same number of domains (stable) or who deteriorated over the course of the two year follow up period (became impaired on more tests, or progressively impaired in one or more domains over the course of the study).

Improvement Stable Stable/Decline Decline

	*NBNF	IBNF	IBLF	IBIF	IBDF	NBIF	IBFF	Total
Controls	22	3	0	1	1	3	0	30
MCI	0	1	4	6	2	0	7	20
SNCI	15	6	1	3	5	2	3	35

*** NBNF Not impaired at baseline assessment and not impaired at follow up**

IBNF Impaired at baseline, not impaired at follow-up

IBLF Impaired at baseline, less impaired at follow-up

IBIF No change in impairment between baseline and follow-up assessments

IBDF Impaired at baseline, different impairment at follow-up

NBIF Not impaired at baseline, impaired at follow-up

IBFF Impaired at baseline with further impairments at follow up

9.2.2.1. Controls

As a group, most individuals who had shown impaired performance on a test at baseline were no longer impaired on this test at follow up. None became impaired on memory tests. None became symptomatic at the end of the study visit and all remained independent in their activities of daily living. Overall 3 subjects developed new impairment over 2 years, this related to scoring beneath the 5th percentile on the TMT, VOSP and the WASI matrices subset. Neuropsychological review did not show any

progressive impairment in any of these domains, and in the case of the individual with impaired performance on the WASI matrices subset, as previous NART and WASI IQ scores were in the lower range, his matrices score was felt to be consistent with this. Shortly after his final visit this gentleman died following a myocardial infarction.

9.2.2.2. SNCI

Most SNCI subjects either maintained or improved their cognitive performance over two years. Of those that did not, four developed memory impairment on either the RMT or CVLT, and two demonstrated progressive impairment on the TMT. All other subjects showed no evidence of cognitive deterioration over their three study visits. Compared to the control group, significantly more SNCI subjects converted to a diagnosis of MCI or AD than the controls ($p=0.024$).

With clinical review, three subjects with memory impairment fulfilled criteria for aMCI by their second study visit, and one fulfilled criteria for AD. One of the aMCI subjects was noted to have had a marked change in personality with the appearance of obsessive tendencies and emotional blunting suggestive of either early frontal variant AD or early FTLD. Of the two subjects who had demonstrated progressive impairment in executive functioning, one was felt to be showing progressive clinical changes but not of a severity to be assigned a clinical diagnosis.

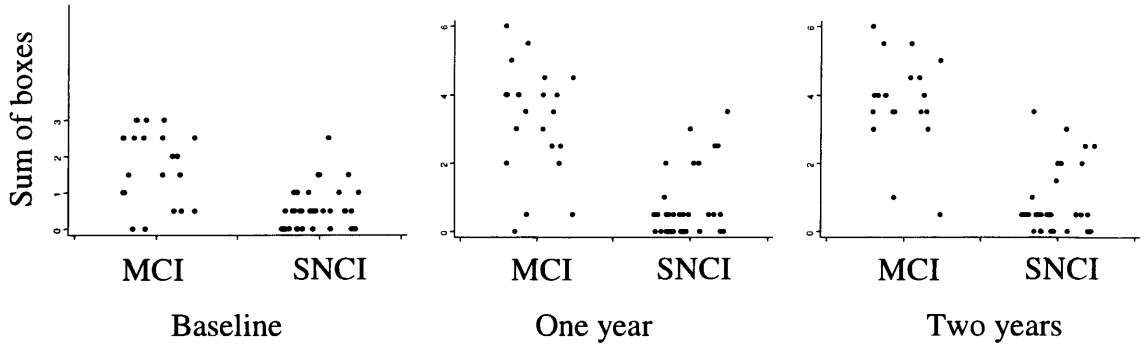
9.2.2.3. MCI

Seven subjects showed progressive cognitive decline over the course of the study. Six of these seven subjects fulfilled criteria for AD. One subject showed progressive decline, but clinically was felt not to fulfil NINCDS-ADRDA criteria for dementia. Two subjects were no longer impaired on tests of memory at two years and reverted to a study diagnosis of SNCI. One further MCI subject declined neuropsychological assessment at two years and had moved into a nursing home.

9.2.3. Change in CDR over one and two years

All subjects had a CDR measured at baseline, one year and two years. Figure 9-1 shows how this measure changed throughout the course of the study.

Figure 9-1 Score on the sum of boxes at baseline, one and two years in the MCI and SNCI groups



9.2.3.1. SNCI

After one year of follow-up a proportion of SNCI subjects demonstrated increasing scores on the CDR (and therefore progressive functional deterioration), whilst the majority of this group remained with low scores. Very little change appeared to have taken place in the CDR over the second year of the study. The highest global CDR achieved at two years in the SNCI group was 0.5, by all four SNCI converters.

9.2.3.2. MCI

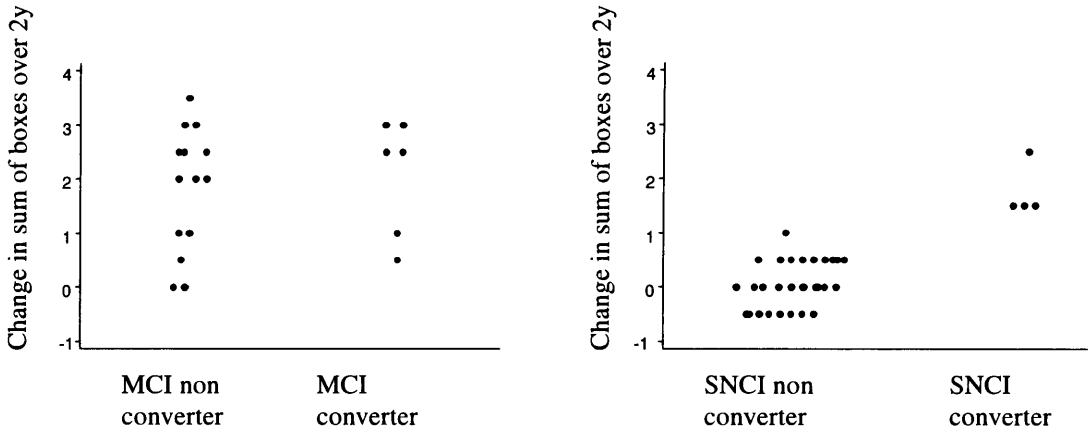
Most MCI subjects increased their score on the CDR over one year. Over the course of the second year, the MCI group as a whole continued to increase their CDR scores, although less dramatically compared to the previous year. The highest global CDR achieved in the MCI group was 1.0, by 4 MCI converters and 3 MCI non-converters

9.2.4. Comparison of outcome one and outcome two

The relationship between the clinical diagnosis at two years, and the change in sum of boxes over two years was different between the MCI and SNCI. In the SNCI there was

evidence of a significant relationship between these two variables ($p<0.001$), but not in the MCI ($p=0.14$).

Figure 9-2 Relationship between change in the sum of boxes over two years and clinical outcome in the MCI and SNCI groups

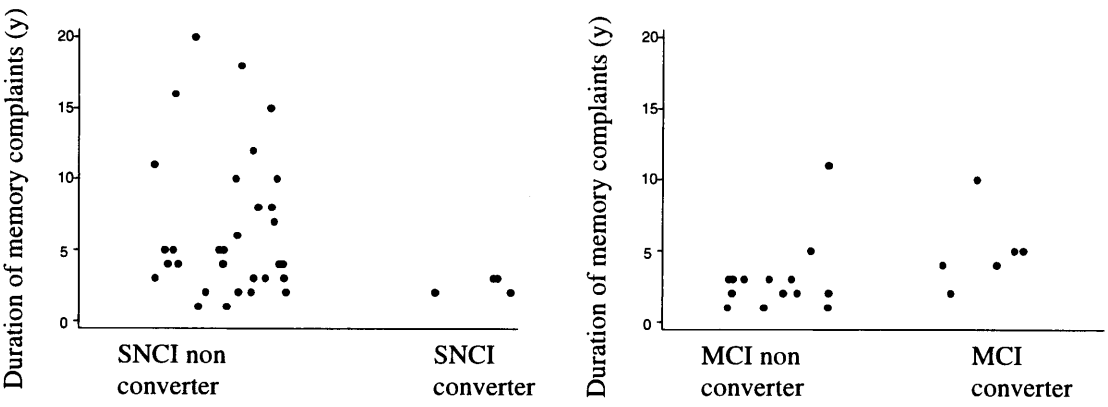


9.2.5. Descriptive characteristics and outcome

There was no evidence of a relationship between subjective complaints, informant rating, use of memory aids or duration of memory complaints and either outcome 1 or 2, in either the MCI or SNCI group. SNCI converters did however appear to have a shorter duration of memory symptoms than those who did not convert but this was not significant ($p=0.13$) (Figure 10-2).

There was no evidence of a relationship between education or age and either outcome.

Figure 9-3 Relationship between duration of memory complaints and clinical outcome in the MCI and SNCI groups



9.2.6. Apolipoprotein E status

One SNCI converter was homozygous for apolipoprotein E4, one was heterozygous (E3, E4) and the other two were homozygous for E3. Of the MCI converters, three were heterozygous (E3,E4) and three were homozygous for E3.

Table 9-4 Anticholinesterase use throughout the course of the study

Showing at what point in the study subjects started treatment with donepezil

	At Study entry		Year 0-1		Year 1-2		Year 2-3	
Group	SNCI	MCI	SNCI	MCI	SNCI	MCI	SNCI	MCI
Number	0	3	0	5	1	0	1	4

9.2.7. Anticholinesterases

Thirteen subjects with MCI commenced and were maintained on Donepezil (an anticholinesterase) for the duration of the study (4 MCI converters), whilst 2 SNCI (both SNCI converters) did likewise. Medication was either prescribed through the cognitive disorders clinic or privately. Two subjects with MCI took Donepezil for a period of four weeks but stopped due to side effects (gastrointestinal, and a persistent metallic taste (2 MCI converters)).

9.3. Discussion

These results suggest that symptoms of memory impairment with or without cognitive impairment are associated with future cognitive decline. After 2 years of follow up 30% of the MCI subjects in this cohort had converted to a diagnosis of AD, whilst 12% of the SNCI had converted to either MCI or AD. At 15%, the annual rate of conversion in our aMCI group is consistent with the rate of conversion described by other clinical studies (10-15%)(Lehrner et al. 2005;Petersen et al. 2001). A wider range of rates have been reported by some clinical (32%)(Geslani et al. 2005) and population based studies

(8%) (Larrieu et al. 2002). Like most other longitudinal studies of aMCI, we also found that the majority of MCI subjects who deteriorated were given a diagnosis of AD.

The annual rate of conversion to MCI or AD was 6% in the SNCI group. Limited literature is available for comparison, although two clinical studies following a group of non-demented individuals over a similar time frame reported a conversion rate to AD of 3% per year (Lehrner et al. 2005;van der Flier et al. 2005). A rate of 1-2% is thought to represent the annual conversion of community dwelling elders to aMCI (Petersen et al. 1999). Our higher rate may in part be due to careful subject selection, with exclusion of any subjects with non-neurodegenerative causes for complaints (e.g., psychiatric, vascular or head injury). These findings suggest that individuals presenting to a memory clinic with symptoms of memory impairment are at increased risk of developing cognitive impairment, even after as little as two years. Of interest, although all three SNCI subjects who developed aMCI fulfilled the Petersen criteria, one individual displayed symptoms that would also be consistent with either early frontal variant AD or FTLD. In the latter case, memory complaints could have reflected impaired attention and concentration. This highlights the importance of considering a range of underlying disease processes when assessing an individual with symptoms of memory impairment.

Two subjects (10%) with memory impairment sufficient for a diagnosis of aMCI at study entry improved their cognitive performance substantially over two years. This was not unexpected, as variability in diagnosis has been noted by other studies. Rates for conversion from MCI to 'normal' differ between studies and depend on length of follow-up, extent of neuropsychological testing, how impairment is defined and MCI subtype. Rates as high as 43% per year have been found in some population studies (Larrieu et al. 2002), whereas in others this has been as low as 2% per year (Busse et al. 2006). Low annual rates have also been found in some clinical studies (Geslani et al. 2005), although overall a conversion rate of 10% is thought to represent that usually found in clinically based studies (Petersen 2004).

In addition to fluctuation in amnestic impairments, non-amnestic impairments were also dynamic. This was of particular interest in the control and SNCI groups, where according to the revised MCI criteria (Petersen 2004) these subjects would have fulfilled diagnostic criteria for single domain non amnestic MCI at study entry. Even

allowing for impairments secondary to restricted knowledge of English (in our subjects who had English as a second language) a sizeable proportion of subjects still fell into this group (11 subjects (3 controls, 8 SNCI non converters)). It is not unusual for this to be the case, and other groups have also found baseline cognitive impairments within their 'normal' cohort (Saxton et al. 2004). Numbers affected vary widely depending on the extent of neuropsychological testing and how existing criteria for aMCI are applied (Alladi et al. 2006). Regarding long-term outcome for each MCI subtype, it has been postulated that in the single domain non-amnestic MCI at least, outcome is more benign, with progression to dementia more likely in aMCI (Busse et al. 2006;Fischer et al. 2007;Silveri et al. 2007). In this context, the presence of an episodic memory deficit may predict disease evolution, while the presence of a disorder in a non-memory domain might still be compatible with healthy ageing (Silveri et al. 2007).

Our second outcome measure, change in the sum of boxes over 2 years, was significantly related to progression to aMCI or AD in the SNCI. This suggests that the SNCI are heterogeneous in terms of underlying disorders, with a proportion in the early stages of a disease process showing increasing functional impairment, whilst others are ageing normally, showing no change in functional abilities over time. By contrast there was no evidence of a relationship between a change in the sum of boxes and clinical diagnosis at 2 years in the MCI. This may not be entirely surprising, as these two outcomes are not interchangeable. The CDR provides a measure of disease severity but does not embody the criteria required to make a diagnosis of AD. For example at any one particular CDR level it is possible to have a combination of diagnoses, a global CDR of 0.5 is compatible with a diagnosis of worried well, aMCI and AD (Petersen 2006). A high sum of boxes in some studies will lead to a subject being classified as declining, whilst if a clinical diagnosis had been used there may have been no change to that subject's clinical status. Where used as an outcome, conversion rates from MCI to AD (CDR0.5 to CDR 1) have often differed markedly from those reported based on actual clinical diagnosis (Daly et al. 2000), and can cause confusion in interpreting or applying the current literature on MCI (Petersen 2004). In recognition of this, several studies have favoured a combination of CDR and clinical information (Grundman et al. 2004;Storandt et al. 2002). In our aMCI group, it is likely that the majority have an underlying neurodegenerative process, which is affecting them at different rates. The result is that most are experiencing a decrease in function over time, but the rate at which this is happening is not necessarily linked to likelihood of a diagnosis of AD.

There was no evidence of a relationship in this study between the number of informant or subjective memory complaints and outcome in either group. Duration of symptoms seemed to be relatively low in all those who converted to a diagnosis of MCI or AD; however, the relationship between outcome and duration of complaints was not significant. Our inability to find an association may be a reflection of the small numbers in this study; alternatively, the quantity of these symptoms may not necessarily be a good marker of the presence of an underlying disease process. Daly et al suggest that complaints related to difficulty with household tasks (e.g., cooking) are associated with cognitive decline, whereas questions directly related to memory (such as forgetting appointments or using list) are common to individuals who will develop AD as well as those ageing normally (Daly et al. 2000). Alternatively, our period of follow-up may not have been sufficient to identify correctly the number of subjects in this study who will go on to develop neurodegenerative disease. Follow-up in other studies has taken place over a longer period of time (Elias et al. 2000;Saxton et al. 2004;Visser et al. 2006) and in some cases up to 22 years (Elias et al. 2000). Visser et al found that individuals continued to convert to a diagnosis of dementia throughout the 10-year follow up of their study (Visser et al. 2006). As such further follow up of this cohort is of great interest.

There was no relationship between age, education or ApoE genotype and conversion to a diagnosis of either MCI or AD in either group. All three variables have previously been reported as risk factors (see chapter 1.7), but perhaps as a result of limited study size or follow-up, were not shown to have had any effect in our cohort.

One potential limitation to this study could have been the initiation of anticholinesterases in a number of subjects throughout the study. In the SNCI only 2 SNCI converters were started on treatment and still fulfilled criteria for MCI and AD at the end of the study. In the MCI, four converters and nine non-converters were commenced on anticholinesterases. Despite initiation of this medication our conversion rate to AD as discussed earlier is still within that expected for a clinical study. It is possible that as clinical diagnosis relied heavily upon demonstration of progressive cognitive impairment, our ratio of MCI converters to non-converters at 2 years might have been different in the absence of anticholinesterase treatment. Initiation of

symptomatic treatment, however, is inevitable in longitudinal studies of this nature, and as such more closely represents the 'real life' clinical course of aMCI.

9.4. Summary

In summary, we have shown that memory complaints in the absence of memory impairment are predictive of future cognitive decline, although only in a proportion of those who complain. Our rates of conversion to clinical diagnosis are consistent with those reported in the current literature.

There was no evidence that either quantity of informant or subjective memory complaints or duration of complaints were associated with progressive cognitive decline. Neither was there a relationship between ApoE genotype, education, age and outcome.

10. Longitudinal neuroimaging

10.1. Introduction

MRI scanning was carried out at baseline and one year. All images were acquired using the same 1.5 Tesla scanner. The first part of this chapter outlines a number of problems that emerged during analysis of these data and discusses how these were surmounted. The following section reports the longitudinal imaging results from this study together with an outline of the statistical methods used.

10.2. Neuroimaging analysis in the pre MCI cohort

Sensitive and accurate neuroimaging is a prerequisite for detecting the subtle changes seen in the early stages of a neurodegenerative disease. For this, it is essential to acquire good quality images with minimal artefact that can be registered together to give the best possible measurement of annual rates of atrophy. In our cohort there were two main areas which could have potentially compromised the accuracy of our results, the quality of individual scans and problems of compatibility for BSI after registration.

10.2.1. Quality of individual scans

As discussed in section (5.2.3) there are a number of factors which can affect the quality of a single scan. In our series individual images were most commonly affected by movement artefact (see Figure 10-1). Steps taken to minimize this included ensuring the comfort of the patient in the scanner and his or her understanding of the scan process. If at the time of image acquisition it was clear that movement had compromised the quality of the scan, the sequence was repeated. In total four scans were sufficiently affected by movement to require exclusion from the study.

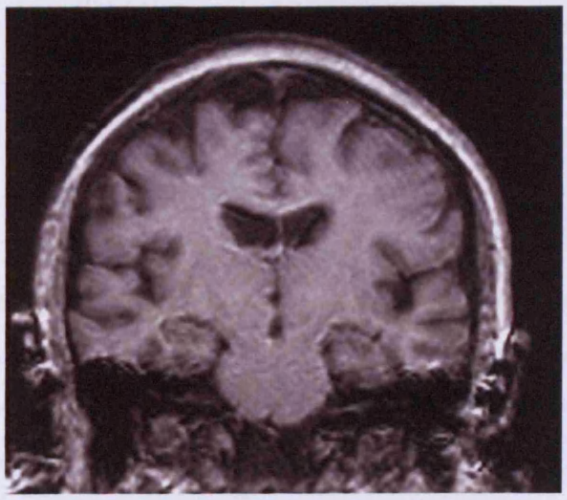


Figure 10-1 A coronal MR image showing movement artefact

10.2.2. Quality of scan pair registrations

10.2.2.1. Registration distortion

As explained in chapter 5, registration of two images taken at different time points allows accurate comparison of the images and whether any atrophy has taken place. There are a number of reasons why this registration process may not appear to work correctly; these include where one image has a different intensity on one part of the scan, or contrast to the subsequent image, or where a sizeable amount of movement is present on one or both images. In our study, we found that an additional problem affected our registrations. Despite excellent scan quality at both baseline and follow-up, several scan pairs, when registered, appeared 'warped', with the brain image stretched relative to the baseline along the anterior-posterior axis. This stretch greatly affected how the BBSI was measured and visualised and therefore the subsequent atrophy quantification. The next section describes this problem in more detail and the steps taken to resolve it.

10.2.2.2. Image warping

Throughout the second year of this study, baseline and one-year follow-up scans underwent whole brain segmentation and registration with subsequent calculation of the

annual rate of atrophy. When the registrations were reviewed, it became apparent that although the registration sequences were running correctly, when the baseline and one-year registered images were compared substantial 'stretching' of the images was taking place between scans. This stretching was non-linear and appeared most commonly along the anterior-posterior axis. This non-linear warping was easiesr to visualise in the sagittal view than in the coronal plane. Consequently, when the BBSI was used to calculate the amount of atrophy present, it was not possible to distinguish between change in brain volume due to this artefactual non-linear stretch or due to cerebral atrophy. Figure 10-2 shows an image from a scan an individual which shows significant change (in red) however this is almost entirely due to stretch between the scans. From the 56 scans originally reviewed at the time of detection of this distortion, 21 were deemed to be sufficiently affected to require rescanning.

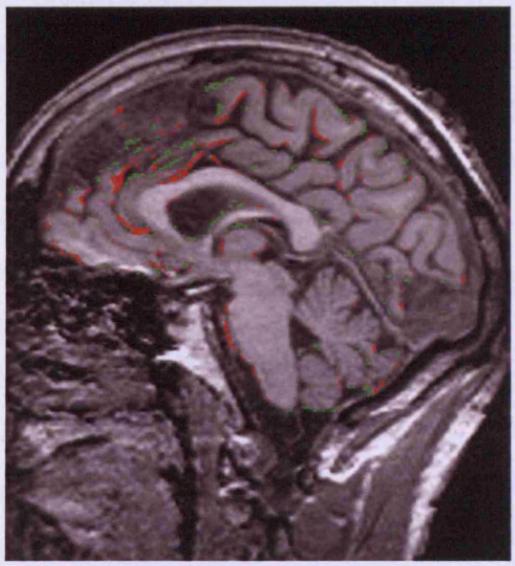


Figure 10-2 Effect of non-linear warp or 'stretch' on the BBSI in a control subject

Areas of green indicate there has been expansion over one year and red showing areas of contraction. These mainly relate to the distortion present as a result of the gradient warping or 'gradwarp'.

10.2.2.3. Gradient warp

The spatial position of a voxel is encoded by its position within the gradient of the magnetic field. Ideally this gradient would be linear and therefore the same throughout the length of the magnet. In reality this is not the case, and there is a certain amount of

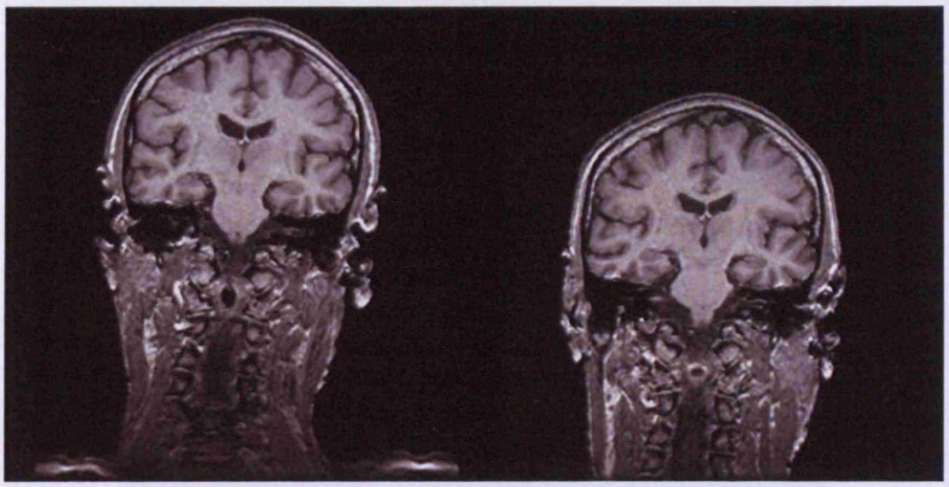
spatial distortion within the scanner. This distortion is centred around the 'isocentre' of the magnetic field and increases with increasing distance from the isocentre.

This distortion does not interfere with the usefulness of this MRI scan when it is obtained for clinical purposes. However, when used for longitudinal analysis this distortion can render the registration unusable.

10.2.3. Solutions to scan registration appearances

10.2.3.1. Positioning within the scanner

To examine which factors contributed to the amount of non-linear stretch present on registration, all scans acquired were reviewed and their registrations compared. This comparison revealed no differences in scan acquisition or registration protocol between those that exhibited non-linear stretch and those that did not. There was no temporal variation seen with this artefact, as both scan pairs acquired at the start of the study, and those obtained some months later were equally affected. This suggested that a change in scanner software or apparatus was not likely to be the cause. As more scans were reviewed, however, it became clear that the position of the subject's head within the scanner did vary between subjects, and that where there was a difference in head position between the baseline and follow-up images a greater degree of stretch was present. Figure 10-3 shows one such scan pair that was affected in this way with subsequent distorted registered images.



Baseline image Repeat image

Figure 10-3 Two scans of the same control subject acquired at a one-year interval but in different positions within the scanner

This distortion meant that the registered image (Figure 10-4) showed areas of expansion (green) and contraction (red) that were not related to a change in brain tissue but were instead related to where non-linear stretch was taking place.

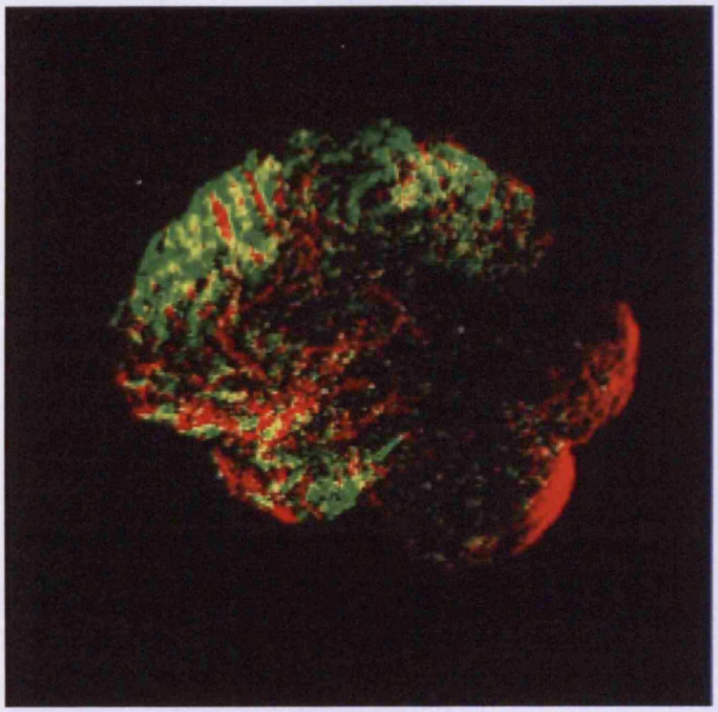


Figure 10-4 BBSI following registration of the two images in figure 10-3

Again the areas of green and red indicating expansion and contraction, mainly relate to the distortion present as a result of 'gradwarp'.

10.2.3.1.1. Field of view

The number of possible positions in which the head can be placed within the scanner depends upon a number of factors. These include how the radiographer ensures consistent patient placement (e.g., by aligning the patient and scanner using an anatomical landmark) and the dimensions of the reconstructed image (given by the field of view (FOV)). Enlarging the FOV decreases the likelihood of matching head position within the scanner from one year to the next. This appeared to be very important, as when we compared the registrations that were unusable due to distortion with those which were unaffected, the difference in position of the head within the FOV between baseline and follow-up images was greater in the affected cohort (Figure 10-5). From the figure it is clear that this is an important factor but not the only influence.

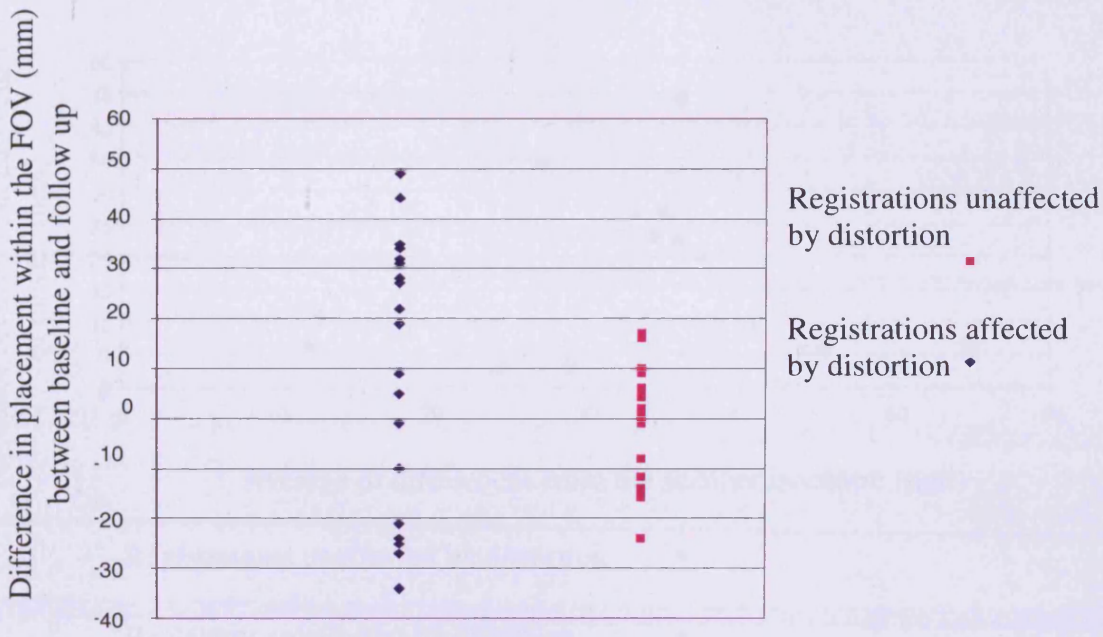


Figure 10-5 Variation of head placement within the field of view

Between baseline and follow up for those registered pairs that were affected and unaffected by the non-linear distortion. Variation in head placement for each scan pair was compared through measuring the distance between the top of the skull and the top of the FOV for each scan.

Consistency in positioning seemed to improve quality of registration; however, it was not clear whether it was consistency in position between years which was important, or if the position in the scanner could vary between years, as long as the distance from the isocentre remained relatively constant.

10.2.3.1.2. Position in relation to the scanner isocentre

Information from scan segmentation was used to give the location of the centre of brain mass in voxel coordinates. An affine transformation given by the scan headers was applied to these coordinates to give the true centre of mass with respect to the magnet isocentre, i.e., the origin. A subgroup of scans was selected from the registrations already obtained from our cohort. This comprised ten registrations of poor quality demonstrating a significant amount of stretch and four registrations with minimal or no stretch present. The difference between the locations of the brain centres of mass in each scan pair was plotted against the average of their respective distances from the scanner isocentre as shown in figure 10-6.

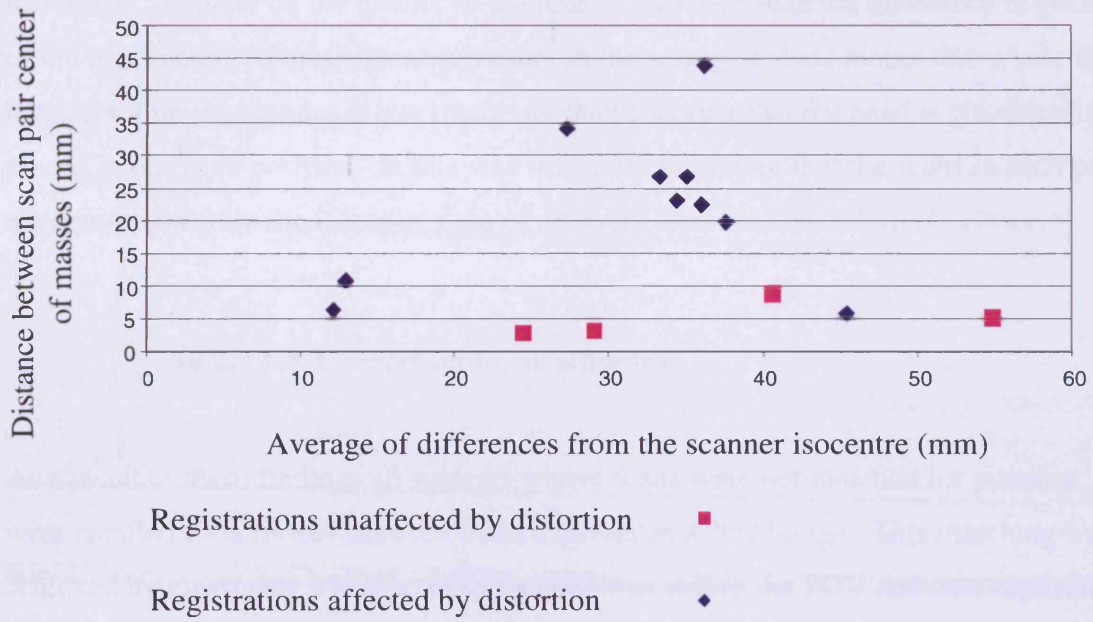
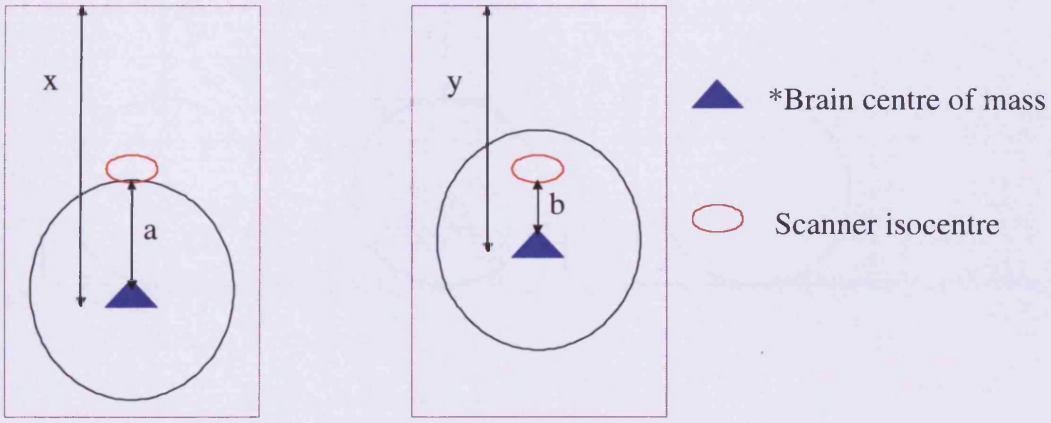


Figure 10-6 The effect of distance from the scanner isocentre and difference in position on quality of scan registration



(x-y)	=	Distance between scan pair centre of masses (mm)
(a + b)/2	=	Average of differences from the scanner isocentre (mm)

Figure 10-7 How different components of Figure 10-6 were calculated

*** Brain centre of mass was defined as the average xyz position of all voxels identified in an individual's whole brain segmentation.**

Figure 10-6 demonstrates that the distance of the brain centre of mass from the isocentre had less of an effect on the quality of the scan registration than the difference in position of the brain centre of mass from each other in the scan pair. This means that where the head is within the scanner is less important than ensuring that the head is consistently placed in the same position. In this way it is more important that the scans in each pair are equally far from the isocentre than of different distances but relatively closer.

10.2.3.1.3. Correction for positioning

As a result of these findings all subjects whose scans were not matched for position were recalled for a further scan to obtain a further matched image. This matching was achieved by measuring where a subject's head was within the FOV and then replicating this for his or her subsequent scan (Figure 10-8 shows how this was achieved in practice).

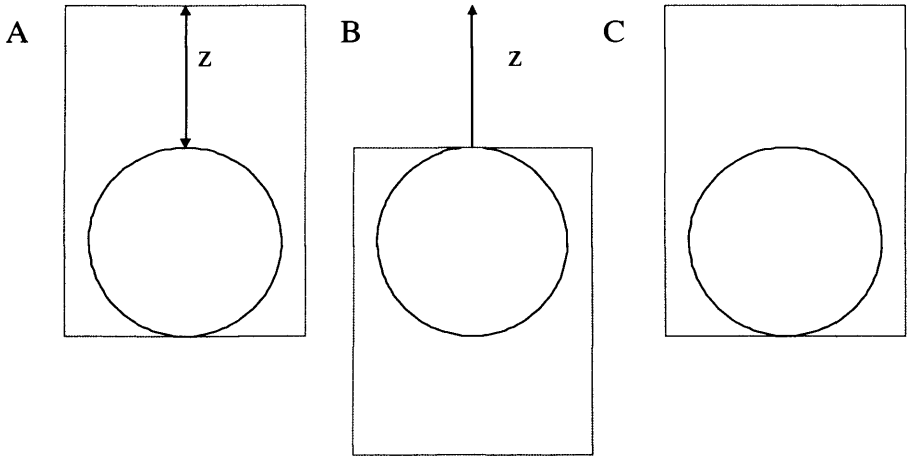


Figure 10-8 How consistency of head placement within the field of view of the scanner was achieved over time

A: Baseline scan, difference between highest point of skull and top of field of view box measured (z).

B: Follow up scan, using the scout scan, the field of view box is placed on the top of the highest point of the skull and moved distance z

C: Follow up image now within the same place in the field of view box as image one.

Through using this technique we were able to improve the registration quality of 14 of the previously affected images whilst 7 failed to have their quality improved. With review of all 85 registrations acquired after one year, 22 were unaffected by any distortion, 30 showed minor distortion, 13 moderate distortion, but the BBSI was still felt to be reliable, and 19 registrations showed distortion of a severity which would have required them to be excluded from the study. This occurred despite consistent head positioning on both scans.

10.2.3.2. Gradient warp correction

Although consistent positioning of the patient in the scanner at each scan is important and improved the usability of a number of scans in the cohort, a significant number of scans remained distorted with non-linear stretch apparent on scan registration. Having improved our ability to achieve consistency at the time of scan acquisition, our next approach was to implement changes at the image processing stage to increase usability of the scans.

10.2.3.2.1 Background

As explained in section 10.2.2.3 there is a certain amount of distortion seen in the gradient field of the MR scanner. To try and correct this distortion, the actual gradient field needs to be obtained. This can be done experimentally using measurements from a probe containing samples of water at a geometrically known position in known positions within the MR scanner (for a detailed account see Eccles et al 1993, and Janke et al 2004 (Eccles CD et al. 1993;Janke et al. 2004)). Through knowing where the magnetic field is experimentally, and the distribution of the field according to the MR scanner measurements (acquired from the MR image) an error can be calculated (the difference between the scanner and the experimental measurement). This error can then be used to apply a correction factor to voxel intensity and location. The MR scanner vendor is able to supply this experimental information (in the form of a set of spherical harmonic co-efficients) which is then used to calculate the displacements of the voxels from their true positions. These displacements can then be inverted and the voxel field resampled to obtain a gradient-unwarped corrected scan. Application of this gradwarp

correction results in better registration of scan pairs and in theory elimination of the non-linear stretch seen.

In practice, correction for distortion in two directions is carried out by General Electric scanners by default. However, one dimension is left uncorrected and has potential to distort the appearance of the registrations. Through application of the vendor supplied coefficients, described above, to the third, uncorrected dimension, a fully three-dimensional grad warp (3D-gradwarp) corrected image was achieved.

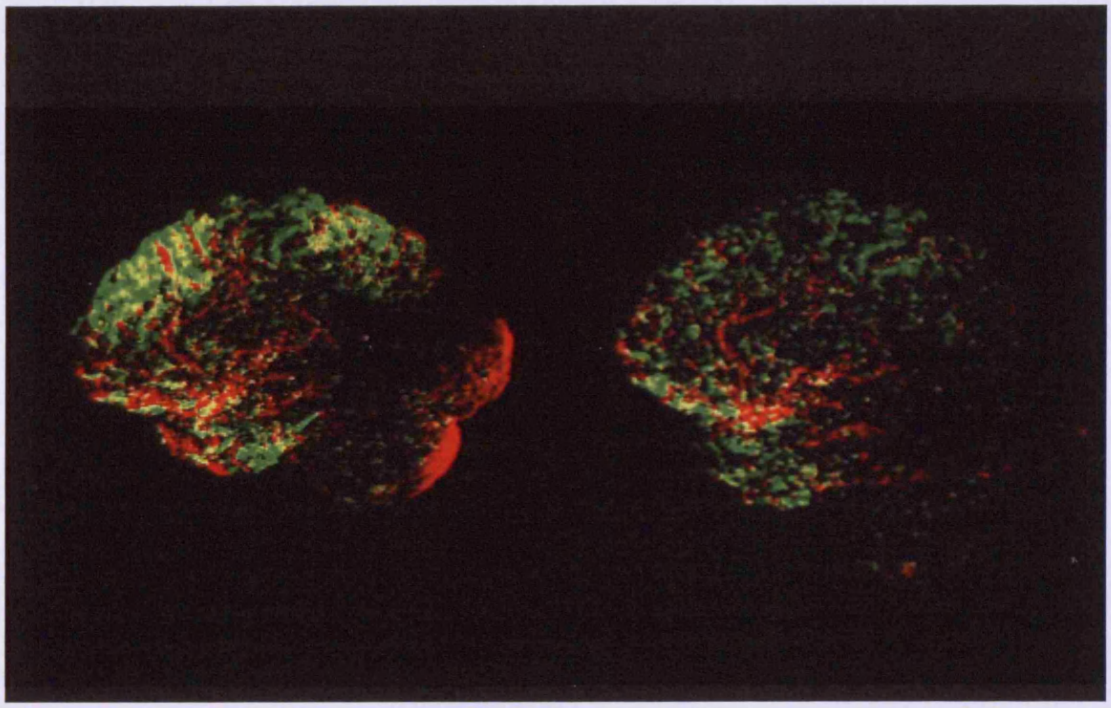


Figure 10-9 The effect of gradient warp correction on the scans registered from figure 10-3

Gradwarp correction substantially reduces the amount of 'noise' measured by the BBSI as a result of non linear stretch.

10.2.3.2.2 Application to the pre MCI study cohort

Although on an individual basis 3D-gradwarp correction appeared to decrease the amount of change measured which was due to non-linear stretch and not atrophy, it was unclear how the gradwarp correction affected the cohort as a whole. To investigate this further a subgroup of 25 control scan pairs were selected randomly and the 3D-gradwarp correction was applied. Table 10-1 shows the difference made to the mean

annual atrophy rate for this group. Figure 10-10 shows the range of atrophy rates when 3D-gradwarp correction was applied and when not. The difference between the groups was not significant (p=0.65).

Table 10-1 Mean annual whole brain atrophy rates with and without gradient warp correction

	Mean Annual Atrophy (%)	SD	Min	Max
Without GWC	0.83	0.82	-0.42	2.66
With GWC	0.68	0.82	-0.62	2.57

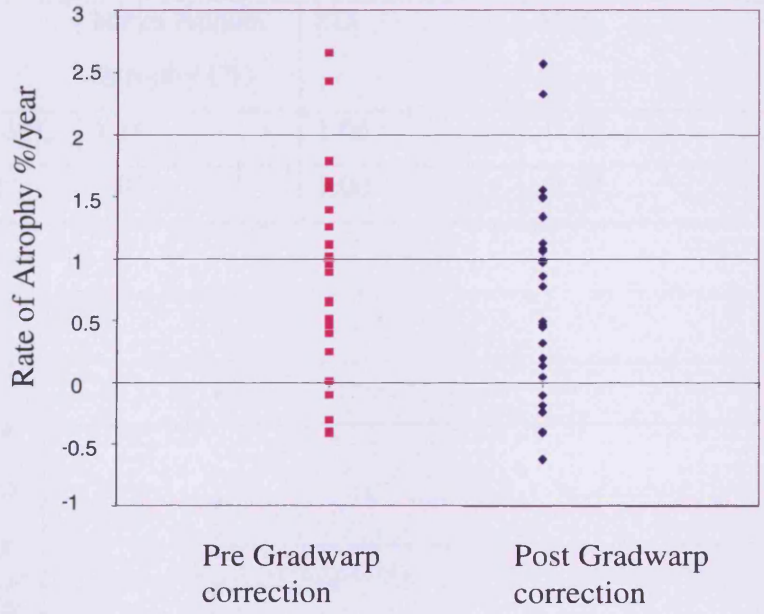


Figure 10-10 Distribution of the annual rates of atrophy in a subgroup of healthy volunteers with and without gradient warp correction

As can be seen from figure 10-10 although the 3D-gradwarp has improved several scans visually, the overall BBSI measurements have not changed substantially. This may be because the non-linear stretch creates an equal amount of artefactual expansion and contraction in the registered images and as a result these two effects cancel each other out.

10.2.3.2.3 Changes to rates of atrophy in the MCI group as a result of gradient warp correction.

Although as shown above, the 3D-gradwarp correction did not significantly alter the BBSIs in the control group, it was important to ensure that this correction did not remove atrophy in the MCI group. We randomly chose a sample of 14 subjects from the MCI group and compared the rates of atrophy pre and post 3D-grad warp correction. As before there was no significant difference between the pre and post 3D-gradwarp corrected annual atrophy rates (p=0.79) (Table 10-2 and Figure 10-11).

Table 10-2 Change in mean annual whole brain atrophy rates with application of gradwarp correction to the MCI sub cohort

	Mean Annual Atrophy (%)	SD	Min	Max
Without GWC	1.16	1.06	-0.42	3.26
With GWC	1.05	1.00	-0.37	3.11

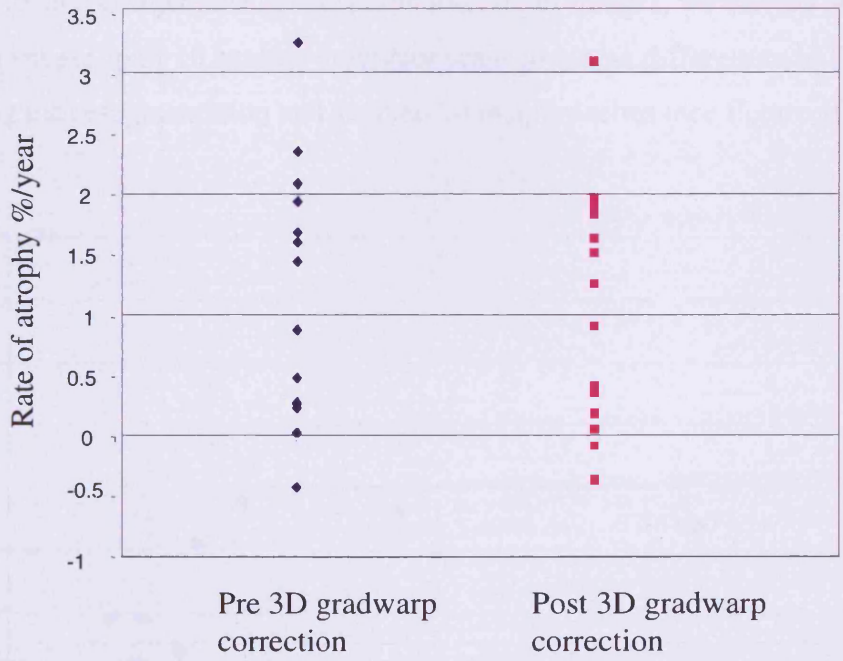


Figure 10-11 Distribution of annual rates of atrophy in the MCI cohort, with and without gradient warp correction

When all scans registrations were reviewed after 3D-gradwarp correction, the number of scans exhibiting non-linear distortion was reduced from 62 to 11 with only five excluded from further analysis, with this being due to a combination of non-linear distortion as well as contrast differences. Based on the visual improvement of the scans as well as increasing the number of scan pairs acceptable for use within the study, it was decided to use the 3D-grad warp correction on the whole cohort.

10.2.3.2.4 Application of gradient warp correction to the cohort

Gradwarp correction was applied at a stage when the majority of annual and follow-up scans from the PreMCI study had undergone whole brain segmentation. As 3D-gradwarp correction could potentially change the form of the image acquired, all segmentations had to be transformed and reviewed to ensure that the segmentations were still correct. An alternative to this approach would have been to resegment all images, although this would have required significant time and resources. To ensure that editing of whole brain segmentation after 3D-gradwarp correction was of sufficient quality and comparable to resegmentation of all images, we carried out both techniques on a subgroup of 10 healthy volunteer scans to assess differences in brain volumes using the resegmentation and segmentation approaches (see Figure 10-12).

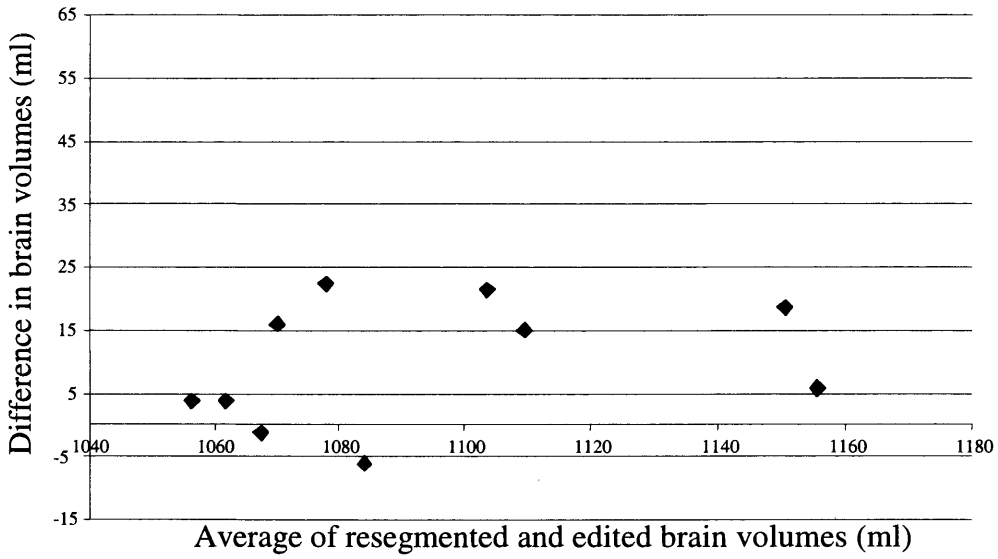


Figure 10-12 A Bland Altman graph showing the difference between resegmentation and editing of brain volumes pre and post gradient warp correction.

There was evidence of bias (p=0.01, paired t-test), but no evidence of a difference in variability (p=0.8, Pitman's test). However the overall difference in measurement of brain volumes using one technique compared to the other was small (mean 9.9 ml, standard deviation 10.0), and as such this method was considered sufficiently reliable to be carried on the whole scan cohort following 3D-gradwarp correction. All ventricular and hippocampal segmentations were carried out on gradwarp corrected images.

10.2.4 Further causes of registration distortion

The combination of patient positioning and 3D-gradwarp correction improved the quality of our registrations and reliability of our data. However, as can be seen from Figure 10-6, it is possible to position the head at similar distances from the scanner isocentre at both baseline and follow up, apply 3D-gradwarp correction and yet still obtain a distorted registration. Such was the case for three scans within that cohort. Careful inspection of these three registrations revealed that two scan pairs showed significant 'drop out' of signal on the follow-up images that was not seen in the baseline scan. In one scan this was due to the presence of failure to remove a dental plate and in the other, metal in a dress collar.

10.2.4.1 Differential susceptibility caused by metal work

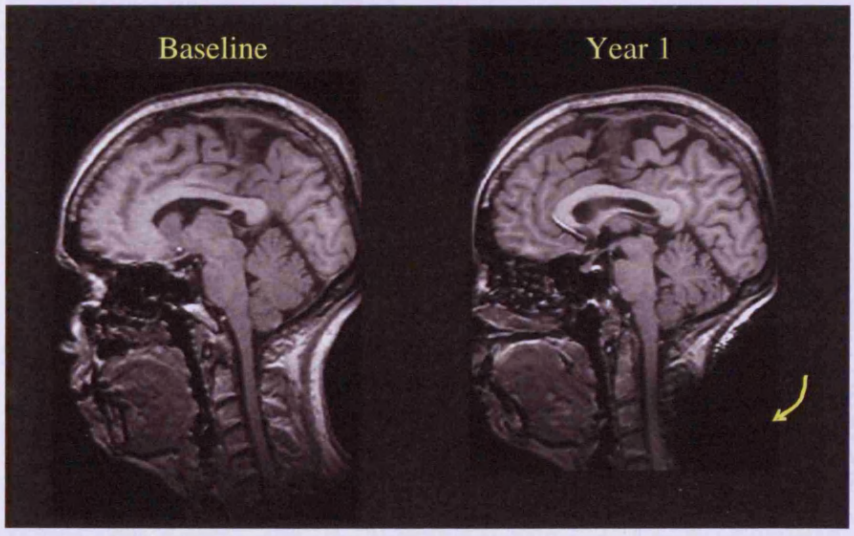


Figure 10-13 Signal drop out between images taken at a one-year interval due to a metal object on a dress label

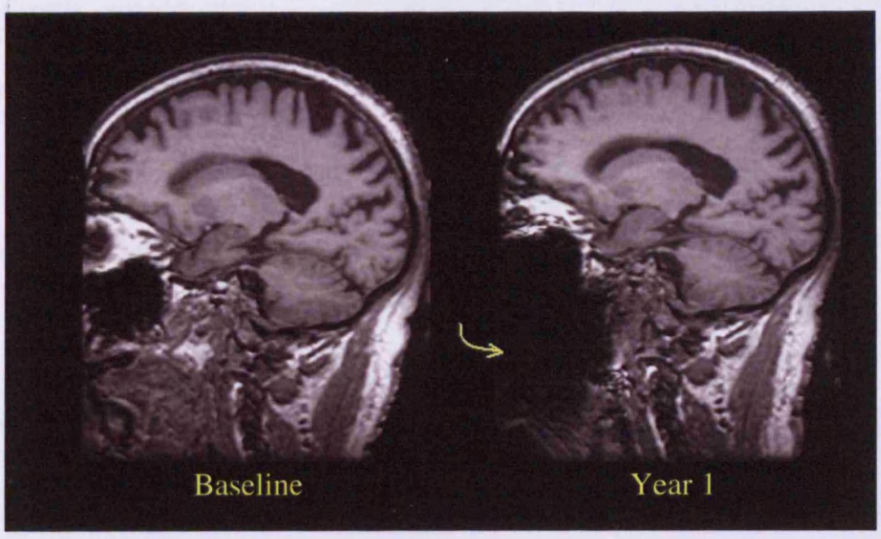


Figure 10-14 The effect of insertion of a dental plate on image signal intensity at follow-up

10.2.4.2 Differential susceptibility caused by changes in head rotation

The final registered pair showing distortion in registration revealed a difference in positioning in the anterior posterior plane. Rotation of the head between scans can distort the uniformity of the magnetic field in that axis, due to different tissue magnetic susceptibility (Figure 10-15). Where metal work is present on both scans, or air is present intranasally, rotation between baseline and follow up scans can therefore cause a susceptibility artefact manifesting as distortion on the registered images.

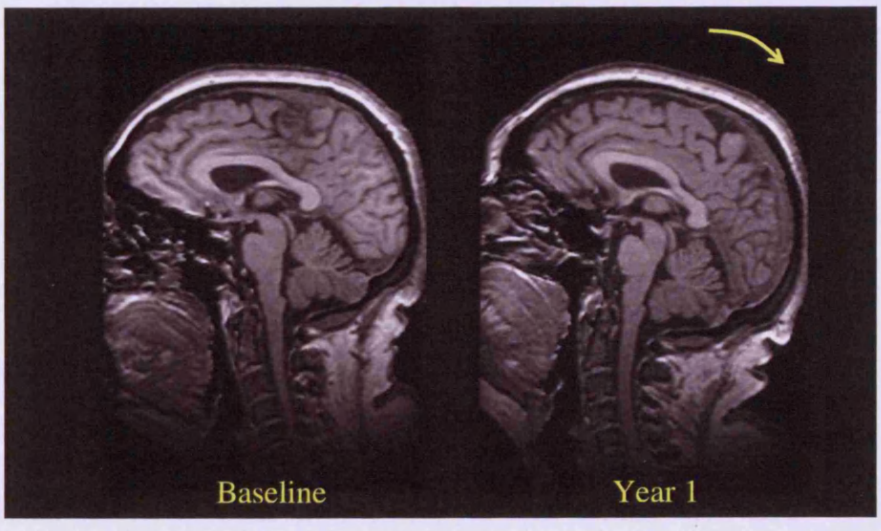


Figure 10-15 Distortion artefact with scan pair registration caused by head rotation

New developments in scanner software have led to the ability to allow an element of rotation to be introduced coronally in the pre scan acquisition set-up phase, known as 'obliquing the volume'. In this case this software would have been able to reduce the effect of the rotation seen between these two scans. However this method could potentially introduce additional distortion to registrations if each scan is adjusted independently of the other and therefore must be used consistently.

10.2.5 Conclusion

Magnetic field non-uniformity and the differential positioning of subjects within this field can cause significant non-linear (geometric) distortions following linear registration. The effect of this distortion can be minimised by both ensuring consistency in patient position in the scanner between baseline and follow up scans and by applying a gradwarp correction as a post processing step.

10.3 Statistical Methods

Linear regression models were used to investigate the differences in means between each group and the associations between rates of whole brain, ventricular and hippocampal atrophy and outcomes one and two. All these analyses were carried out using robust standard errors.

10.4 Results

10.4.1 Introduction

10.4.1.1 Subjects

All subjects underwent MR scanning as described in chapter 6. In total, 30 controls, 35 SNCI subjects and 20 MCI subjects had MRI scans at both baseline and one-year visits. Second scans were not obtained on three controls who dropped out after their baseline

visit (see chapter 9), and one MCI subject who declined further neuroimaging as a result of an injury to her back.

10.4.1.2 MRI registration and measurement of volume change

MRI registration methods are detailed in section 6.4. In brief, all scans were transferred to a Sun Workstation and pre-processing steps carried out, including gradwarp correction, and N3 correction. Trained segmentors then edited previously acquired whole brain regions to ensure that all outlined regions were accurate. Whole brain volumes were corrected with a single measurement TIV to provide cross-sectional correction for differences in head size. These whole brain segmentations were then registered to each other and dbc applied. In order to calculate rates of whole brain atrophy the BSI was used to assess change in brain volume over time.

All ventricular and hippocampal segmentation was carried out using gradwarp corrected images as previously described. Change over time was measured for ventricular volumes using subtraction of serial measures. The BSI was used based on the baseline hippocampal region to calculate hippocampal volume change.

10.4.1.3 Scan pair selection

All registrations were reviewed by two trained researchers (HA and JB or HA and SP). Each scan was assessed for overall quality in terms of contrast differences between the scans and the presence of any movement artefact. Registration of each scan pair was then reviewed and overall quality again noted. As a result of this process, 18 scan pairs were excluded from the whole brain atrophy measurements, 16 from ventricular measurements and 8 from the hippocampal measurements. The main reasons for excluding scan pairs were image artefacts with resultant BBSI measurement distortion (see Figure 10-16), and differing white and grey matter contrast between baseline and follow up images (see Figure 10-17). The subject characteristics and rates of atrophy of the scans excluded were not systematically different from those that were retained. Rates of atrophy were not calculated until the final scan cohort had been selected in order to reduce the risk of biasing inclusion decisions.

Table 10-3 Scan pairs excluded from longitudinal neuroimaging analysis

	Whole brain measurements		**Ventricle measurements**		**Hippocampal measurements**	
Controls	Image artefact	1				
	Contrast Difference	3	Contrast Difference	3	Contrast Difference	1
	Movement artefact	3	Movement artefact	3	Movement artefact	2
	Total	7	Total	6	Total	3
MCI	Image artefact	1				
	Contrast Difference	2	Contrast Difference	2	Contrast Difference	3
	Movement artefact	1	Movement artefact	1		
	Total	4	Total	3	Total	3
SNCI	Image artefact	1			Image artefact	1
	Contrast Difference	5	Contrast Difference	5	Contrast Difference	2
	Total	6	Total	5	Total	3
Total Excluded	17/86		14/86		9/86	

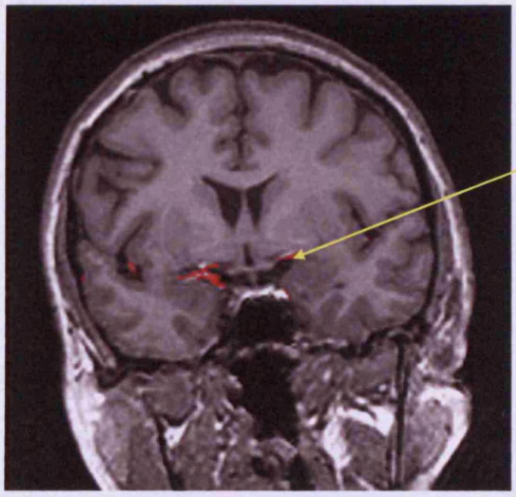
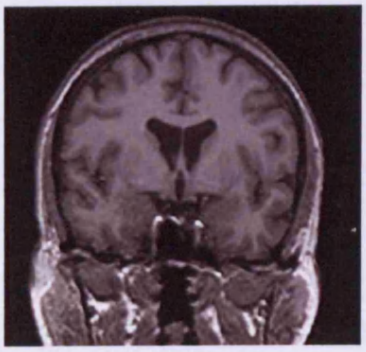
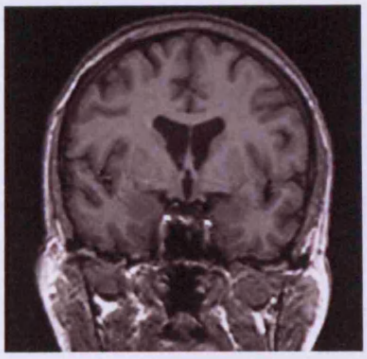


Figure 10-16 Image artefact in a control subject and its effect on the BBSI measurement.

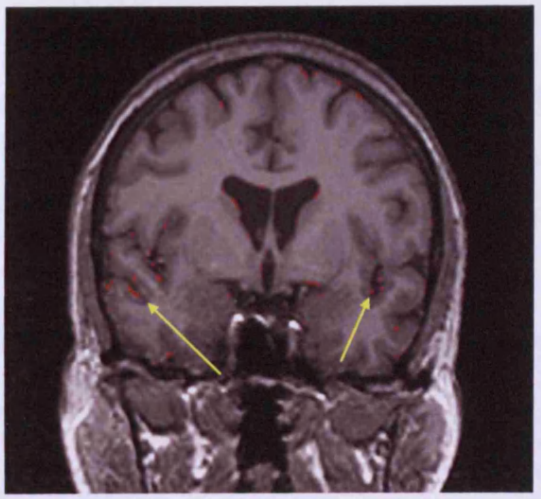
A difference in intensity of these vessels between baseline and follow up scans leads to the BBSI recording an inaccurately high rate of atrophy. Change in contrast between the serial scans may also indicate a difference in image acquisition, which can also lead to erroneous BBSI measurements.



Control Baseline



Control Follow up



Registered images

Figure 10-17 Effect of differing contrasts on baseline and repeat scans.

In this case the lower contrast on the baseline compared to the follow up scan has resulted in an overestimate in the BBSI (yellow arrows).

Table 10-4 Comparison of clinical characteristics of patients included and excluded from analysis

	Brain volume analysis		**Ventricle analysis**	
	Excluded	Included	Excluded	Included
Number	18	68	15	71
Age	61.8 (9.7)	63.7 (8.6)	61.1 (9.9)	63.8 (8.6)
Sex M:F	7:11	36:32	6:9	37:34
Education (y)	13.6 (2.8)	14.4 (2.7)	13.7 (3.0)	14.3 (2.7)
% Ischaemic Heart disease	28	6	27	7
% Diabetes	11	7	13	7
% Cholesterol	50	38	47	39
% Treated Hypertension	33	34	40	32
% With one APOE E4 allele	33	41	40	39
MMSE	29 (1.2)	29 (1.2)	29 (1.0)	29 (1.3)

10.5 Group results

10.5.1 Statistical methods

Linear regression models were used to investigate the differences in means between each group; age was included as a covariate. All these analyses were carried out using robust standard errors to allow for the anticipated differences in variance between groups.

10.5.2 Rates of whole brain and ventricular change by group

Rates of whole brain atrophy were calculated for each group as outlined in the methods (see section 6.4.3). The resultant rates of atrophy are reported in Table 10-5. P-values are given for comparisons between group specific atrophy rates. The mean interval (standard deviation in brackets) between scans for the entire group for whole brain atrophy was 393.1 (64.3) days (controls 409.7days (73.4), MCI 368.4days (29.4), and SNCI 393.6 days (67.9)).

Table 10-5 Rates of whole brain atrophy in the control, MCI and SNCI groups

P-values are given for comparison of the means, and standard deviations are in brackets

	Controls N=23	MCI N=16	SNCI N=29	C v M P value	C v S P value	M v S P value
Whole brain atrophy %volume/y	0.37 (0.39)	1.09 (0.76)	0.46 (0.51)	**0.002**	0.52	**0.006**

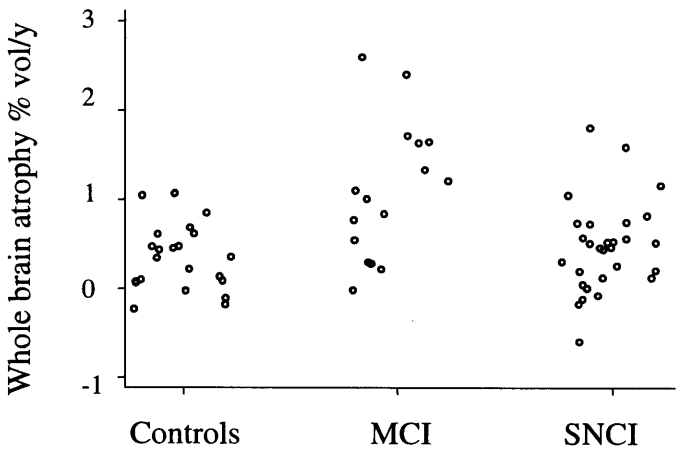


Figure 10-18 Rates of whole brain atrophy in the control, MCI and SNCI groups

The rates of ventricular atrophy for the different groups are reported in Table 1-6. P-values are given for comparisons between group specific rates of ventricular enlargement. The mean interval (standard deviation in brackets) between scans for the whole group for ventricular enlargement was 391.0 (63.0) (controls 405.9 (71.5), MCI 366.9 (29.1), and SNCI 392.4 (67.1)) days.

Table 10-6 Rates of ventricular enlargement in the control, MCI and SNCI groups

	Controls (25)	MCI (17)	SNCI (30)	C v M P value	C v S P value	M v S P value
Rate of ventricular change, ml/y	0.83 (1.56)	3.39 (2.35)	1.4 (2.03)	<0.001	0.23	0.01

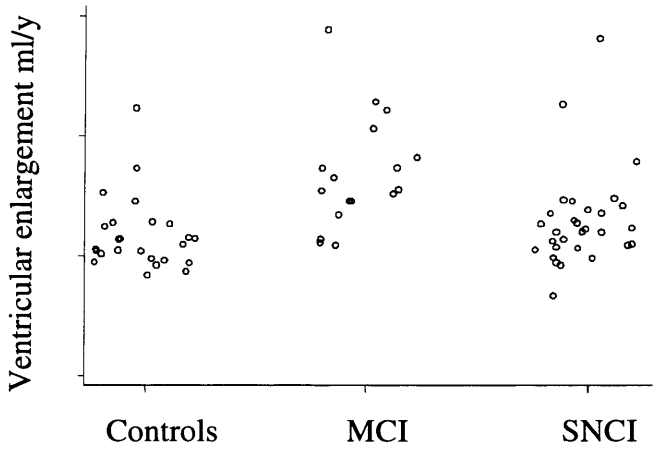


Figure 10-19 Rates of ventricular enlargement in the control, MCI and SNCI groups

10.5.3 Rates of hippocampal atrophy by group

The rates of hippocampal atrophy are reported for each group in Table 1-5. The mean interval (standard deviation in brackets) between scans for the whole group was 391.4 (61.1) (controls 404.4 (68.6), MCI 370.2 (30.1), and SNCI 391.6 (65.0)) days.

Table 10-7 Rates of right and left hippocampal atrophy in the control, MCI and SNCI groups

P-values are given for inter-group comparisons (standard deviations in brackets).

	Controls N=27		MCI N=17		SNCI N=32		C v M P value	C v S P value	M v S P value
Rate of	R	L	R	L	R	L	R	R	R
hippocampal							0.001	0.68	0.006
atrophy	0.75	0.73	2.68	3.07	0.92	0.90	L	L	L
%volume/y	(0.9)	(1.1)	(1.7)	(1.8)	(1.7)	(1.3)	<0.001	0.64	<0.001

***R = right, L = left**

10.5.4 Group results discussion

Overall the rates of atrophy and ventricular enlargement in our control group were consistent with those from other groups. Where our results were slightly lower than Jack et al (Jack, Jr. et al. 2005), this is likely due to the lower age range in our study cohort. Despite this overall consistency, there is a certain amount of variation seen between the rates of atrophy reported across studies. This variability in measurement reflects the difficulties encountered in consistently identifying brain substructures such as the hippocampi (see section 5.4.2.3), as well as methodological differences, technical considerations and age ranges of the subjects involved.

Table 10-8 Rates of change in the control group compared with previously published data

Standard deviations in brackets

	Age y	Rate of whole brain atrophy %volume/y	Rate of ventricular enlargement ml/y	Rate of total (r + l) hippocampal atrophy %volume/y
Archer et al	**~64**	**0.37 (0.4) *N23**	**0.83 (1.6) N25**	**0.89 (1.2) N27**
(Jack, Jr. et al. 2005)	~82	0.5 (0.7) N91	2.4 (2.0) N91	1.7 (1.4) N91
(Wang et al. 2002)	~70	0.4 (0.5) N14		
(Fox et al. 2000)	~65	0.41 (0.5) N19		
(Schott et al. 2005)	~69		1.0 (1.1) N19	
(Wang et al. 2003)	~73			2.3 (1.9) N26
(Du et al. 2004)	~77			0.8 (1.7) N25

***N = study numbers**

Table 10-9 Rates of change in the MCI group compared with previously published data

	Age y	Rate of whole brain atrophy %volume/y	Rate of ventricular enlargement ml/y	Rate of total (r +l) hippocampal atrophy %volume/y
Archer et al	**~66**	**1.09 (0.8) N16**	**3.4 (2.4) N17**	**3.2 (2.4) N17**
(Ridha et al. 2006)	~49	1.8 (0.9) N6		3.4 (1.3) N6
(Jack, Jr. et al. 2005)	~82	0.7 (1.0) N72	3.3 (2.3) N 72	3.3 (2.7) N72

Rates of whole brain atrophy in the MCI fell midway between those expected for normal controls (see Table 1-9) and established AD (2.0%/y) (Fox et al. 2000;Wang et al. 2002). Our results were also reasonably consistent with those reported in the available literature, although both whole brain and hippocampal atrophy rates (taking age into account) were slightly higher than those of a sporadic AD study (Jack, Jr. et al. 2005). One explanation for this difference may be that a greater number of subjects in our cohort have an underlying neurodegenerative disease than in the community-derived sporadic study, and, indeed, our high yearly conversion rate to AD (15%) supports this. By contrast, our rates of whole-brain change were lower than that found in subjects in the familial AD (FAD) study (Ridha et al. 2006). These subjects are likely very

homogeneous in terms of underlying disease, as all were identified carriers of AD gene mutations.

Few studies have been published whose subjects are directly comparable to the SNCI group. Where studies have assessed individuals with normal cognition who then progress to a diagnosis of AD, these groups are most often comprised of 'healthy volunteers' without memory complaints. The mean rate of atrophy seen in our SNCI group was only 20% higher than that of the control group, and not significantly different on statistical testing. This slightly increased rate of atrophy was associated with a higher variance in the SNCI, with the difference in variance between right hippocampal atrophy in the controls and SNCI found to be significant (P=0.0009). This suggests that most SNCI subjects were similar to the controls, but a few outliers had higher rates of atrophy, implying heterogeneity within the SNCI group.

By contrast, rates of whole brain and hippocampal atrophy and ventricular enlargement could all differentiate MCI from controls and MCI from SNCI.

There was one outlier in the control group, a 79-year-old male, who had a rate of ventricular enlargement similar to that found in the MCI group at 6.15ml per year. Corresponding rates of whole brain (1.06 ml/y) and hippocampal atrophy (1.3 (L), 2.8 (R) ml/y) were also high compared to the results for the rest of our control group. This subject was asymptomatic, and showed no cognitive decline or change to his activities of daily living throughout the 2-year follow-up, and therefore remained in the 'healthy control' group. Future follow-up will help elucidate whether this subject went on to develop a neurodegenerative disease at a later stage.

10.6 Relationship between neuroimaging and outcome at 2 years

10.6.1 Statistical analysis

Linear regression models were used to determine whether there was a relationship between neuroimaging changes over one year and outcome at 2 years. The outcome measures in this study were (1) clinical diagnosis at 2 years (clinical rating) and (2) sum of boxes on the clinical dementia rating at 2 years (functional rating) (see chapter 10).

The relationship between neuroimaging and clinical diagnosis was assessed by fitting a model with clinical rating as a binary predictor.

10.6.1.1 Analysis 1 - Change over one year and outcome

Linear regression models were used to investigate the associations between whole brain atrophy, ventricular enlargement, and right and left hippocampal atrophy and each outcome. All analyses for outcome 2 included baseline sum of boxes as a covariate to incorporate a measure of function at the initial study visit. Additional models, which also adjusted for the sum of boxes at one year, were fitted to investigate the temporal nature of the association.

10.6.1.2 Analysis 2 - Cross-sectional measurements and outcome

Linear regression models were used to explore the association between baseline whole brain, ventricle and hippocampal volumes and one-year whole brain and ventricular volumes and either outcome 1 or 2. Where a relationship was found, further regression was fitted, adjusting for the respective rate of atrophy. This provided information on the relative contributions of cross-sectional volumes and rates of atrophy in predicting outcome at 2 years.

10.6.2 SNCI

10.6.2.1 Analysis 1

There was evidence of a relationship between the rate of ventricular enlargement and the extent of hippocampal atrophy between baseline and one year, and outcomes 1 and 2, and a relationship between whole brain atrophy and clinical diagnosis at 2 years.

Table 10-10 Rates of change in the SNCI converters and non-converters

Means are given with standard deviations in brackets.

	Whole brain atrophy %volume/y		Ventricular enlargement ml/y		Total Hippocampal atrophy, %volume/y	
Group	Non-converter	Converter	Non-converter	Converter	Non-converter	Converter
Rate	0.3 (0.4)	1.2 (0.7)	0.9 (1.0)	4.9 (3.7)	0.7 (0.8)	3.8 (2.0)

Table 10-11 Relationship between rates of change, clinical rating and clinical diagnosis (AD or MCI) at two years in the SNCI group.

P-values, coefficients and confidence intervals (in brackets) are given.

	Whole brain atrophy %volume/y	Ventricular enlargement ml/y	Hippocampal atrophy (R) %volume/y	Hippocampal atrophy (L) %volume/y	Year one sum of boxes
Outcome 1 (Clinical diagnosis)	**P<0.001** 0.9 (0.5-1.4)	**P<0.001** 4.0 (2.3-5.6)	**P<0.001** 3.4 (2.0-4.8)	**P<0.001** 2.7 (1.6-3.7)	***P<0.001** 1.8 (1.2-2.4)

***Co-varying for baseline sum of boxes**

Table 10-12 Relationship between rates of change, clinical rating and sum of boxes at two years in the SNCI group.

P-values, coefficients and confidence intervals (in brackets) are given

	Outcome 2 (Sum of boxes)*
Whole brain atrophy	P=0.053
Ventricular enlargement	**P<0.001** 0.2 (0.1-0.3)
R hippocampal atrophy	**P<0.001** 0.3 (0.15-0.35)
L hippocampal atrophy	**P=0.01** 0.25 (0.07-0.44)
Year one sum of boxes	**P<0.001** 0.70 (0.47-0.94)

***Co-varying for baseline sum of boxes**

The statistical significance of the relationships between rates of cerebral change and the sum of boxes at 2 years was lost when analysed in combination with the one year and baseline sum of boxes.

The statistical significance of the associations between whole brain atrophy, ventricular enlargement, left and right hippocampal atrophy and clinical diagnosis (outcome 1) were maintained, however, when analysed in combination with year one and baseline sum of boxes (see table 1-14).

Table 10-13 Rates of change and outcome one and two in the SNCI group

(a) the relationship between rate of change and outcome 1 whilst adjusting for baseline and 1y sum of boxes, and (b) the relationship between 1y sum of boxes and outcome 2 whilst adjusting for baseline sum of boxes and rates of atrophy or ventricular enlargement.

	Whole brain atrophy %volume/y	Ventricular enlargement ml/y	Hippocampal atrophy (R) %volume/y	Hippocampal atrophy (L) %volume/y
Clinical Diagnosis at 2 years, adjusting for sum of boxes at one year	**P<0.001** 1.46 (0.7-2.2)	**P=0.002** 5.18 (2.1-8.3)	**P<0.001** 5.3 (2.8-7.7)	**P=0.002** 3.2 (1.2-5.1)
Clinical Diagnosis at 2 years and sum of boxes at one year, adjusting for each rate of atrophy	**P<0.001** 2.27 (1.6-3.0)	**P<0.001** 2.1 (1.4-2.8)	**P<0.001** 2.3 (1.6-3.0)	**P<0.001** 2.0 (1.3-2.7)

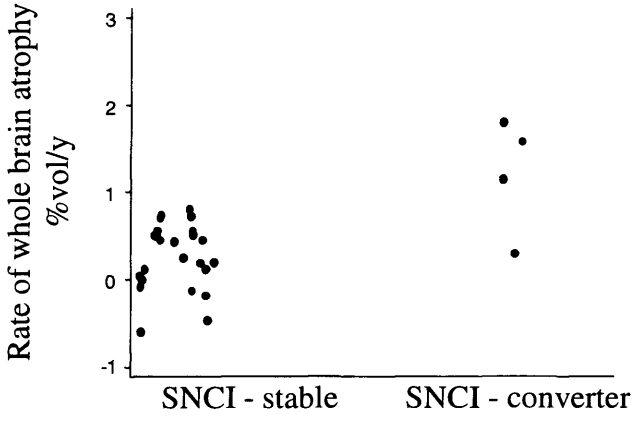


Figure 10-20 Relationship between rate of whole brain atrophy and clinical diagnosis at two years in the SNCI group

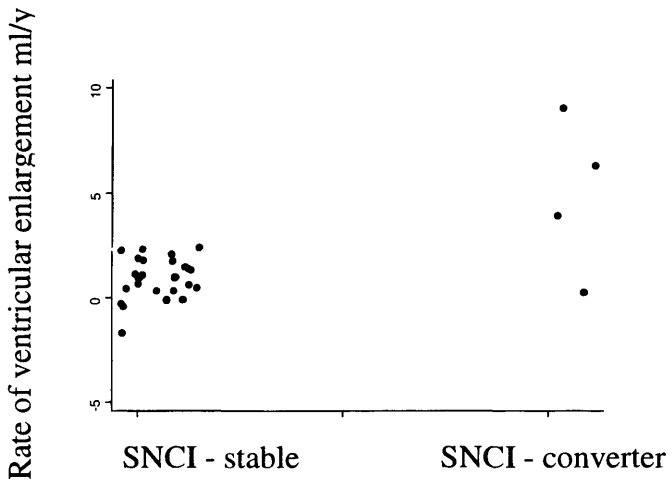


Figure 10-21 Relationship between rate of ventricular enlargement and clinical diagnosis at two years in the SNCI group

10.6.2.2 Analysis 2

There was a statistically significant relationship between baseline ventricular volume, right and left hippocampal volumes and clinical diagnosis at 2 years. There was no evidence of a relationship between whole brain, ventricular or hippocampal baseline volumes and sum of boxes at 2 years. There was a statistically significant relationship between baseline sum of boxes and sum of boxes at 2 years ($P<0.001$, 1.17 r2=0.49 (0.87-1.46). There was no evidence of an association between baseline sum of boxes and clinical diagnosis at 2 years.

When the relationship between baseline volumes and clinical diagnosis at 2 years was adjusted for rates of atrophy, the statistical significance of the baseline hippocampi to outcome decreased, and the statistical significance of the association between baseline ventricular volume and clinical diagnosis at 2 years was lost (see Table 10-14).

Table 10-14: Relationship between baseline volumes, sum of boxes and outcome one in the SNCI group

Coefficients, and confidence intervals (in brackets) are also given.

	Baseline ventricle volumes /cm^3	Baseline R hippocampal volumes /cm^3	Baseline L hippocampal volumes /cm^3	Baseline sum of boxes
Clinical diagnosis	**P=0.022** 20.7 (3.2-38.2)	**P<0.001** -0.8 (-1.2, -0.4)	**P=0.006** -0.7 (-1.1, - 0.2)	P=0.45
Clinical diagnosis Whilst adjusting for rates of atrophy	P=0.527	**P=0.003** -0.9 (-1.4, -0.3)	**P=0.013** -0.8 (-1.4, -0.2)	
Relationship between rates of atrophy and clinical diagnosis whilst adjusting for baseline volumes	P=0.001 2.7 (1.2-4.1)	**P<0.001** 3.1 (1.5-4.8)	**P=0.001** 3.2 (1.5-5)	

There was evidence of a relationship between one-year ventricular volumes and both outcomes, but not whole brain volumes in the SNCI (see Tables 1-15 and 1-16).
When the relationships between one-year ventricular volume and outcome 1 and 2 were adjusted for rate of ventricular enlargement, these relationships were no longer statistically significant.

Table 10-15 Relationship between one-year ventricular volume and outcome one in the SNCI group In comparison to, and in combination with, the rate of ventricular enlargement.

	One year ventricular volume /cm^3	Ventricular enlargement ml/y
Clinical diagnosis (Outcome 1)	**P=0.011** 24.68 (6.0-43.3)	**P<0.001** 4.0 (2.3-5.6)
Clinical diagnosis adjusting for 1y volume* or rate of enlargement+	+ P=0.52	* **P=0.001** 2.4 (1.02-3.8)

Table 10-16 Relationship between one-year ventricular volume and outcome two in the SNCI group In comparison to, and in combination with, the rate of ventricular enlargement

	2 year sum of boxes (Outcome 2)	2 year sum of boxes adjusting for 1y volume* or rate of enlargement+
One year ventricular volume /ml	**P=0.009** 0.01 (0.003-0.02)	+ P=0.24
Ventricular enlargement ml/y	**P<0.001** 0.2 (0.1-0.3)	***P=0.012** 0.29 (0.07-0.51))

10.6.2.3 Summary SNCI

Within the SNCI group, rates of atrophy and ventricular enlargement over one year were significantly associated with both outcomes at 2 years. Only the association between increased rates of change and clinical diagnosis at 2 years maintained significance when adjusted for change in the sum of boxes over one year.
Cross-sectional volumetric measures were also linked to future cognitive decline. Increased ventricular volume at baseline and one year, and decreased hippocampal volume at baseline were significantly associated with clinical decline at 2 years.
The association between cross sectional volume and clinical decline was independent of rate of change in the hippocampi, but not in the ventricles. The association between hippocampal volume and outcome was not as strong as that with rates of hippocampal atrophy.

10.6.2.4 Discussion SNCI

In this study we have shown that, similar to presymptomatic familial AD (Fox et al. 1996;Fox et al. 1999), subtle cerebral changes can be detected when individuals have symptoms of memory loss but no cognitive impairment. Increased rates of change in all our chosen neuroimaging measures were associated with future cognitive decline

.

This finding is consistent with previous work where measures of medial temporal lobe change (Rusinek et al. 2003), hippocampal atrophy (Jack, Jr. et al. 2004;Jack et al. 2000), whole brain (Jack et al. 2000) and ventricular change (Jack, Jr. et al. 2004;Jack, Jr. et al. 2005) have all been found to correlate with progression from 'cognitively normal' to diagnosis of aMCI or dementia. Measures of ventricular change also correlate with neuropathological findings in preclinical AD, and have been found to be a robust marker of both neurofibrillary tangle accumulation and plaque formation (Silbert et al. 2003).

These findings are not consistent across all groups, one recent population study found no association between rates of ventricular change and conversion to aMCI or AD. However, this group employed a different method of measurement to that of our study (ratio of ventricular volume to brain volume), and only a small proportion of their total cohort of population study underwent sequential scans (Carmichael et al. 2007).

There was also evidence of a relationship between baseline ventricular and hippocampal volumes and clinical outcome, but not whole brain volume and outcome. Results from previous work are generally supportive of an association between decreased baseline cerebral volumetric measures and future cognitive decline. Some groups have found a relationship, or trend to a relationship, between reduced hippocampal volume and clinical deterioration (den et al. 2006;Jack et al. 2000); others have found the same for whole brain volume (van der Flier et al. 2005). One group found no association between cross-sectional medial temporal lobe volumes and outcome (Rusinek et al. 2003) and suggested that rates of change had a stronger association with clinical outcome. Our results suggest that baseline hippocampal and ventricular volumes as well as their respective rates of change are both associated with cognitive decline at 2 years. Overall, however, rates of change are more important than absolute volumes, especially where a large natural variation in volume of these structures may be present.

We also assessed the possibility that cross-sectional whole brain and ventricular volumetric measurements derived from the second sequential MRI scan might already contain most of the predictive information found in the rates of change measurements. We found that only the ventricular measurement at 1 year was associated with future cognitive decline, and this relationship lost its significance once adjusted for rate of ventricular change. This would suggest that rates of change (at least in the ventricle) provide additional information to that given by a one-off measurement at either one or two years. This finding also supports the use of serial MR scanning in individuals with symptoms of memory impairment who may be at risk of future AD.

Finally, we repeated the above analysis whilst adjusting for the change in clinical function (measured by the CDR) that had occurred over one year. This was to assess whether neuroimaging provided information additional to that which could have been gained through administering this clinical rating. The relationship between rates of atrophy over one year and clinical outcome (at two years), but not the sum of boxes at 2 years, was maintained even after adjusting for the change in CDR rating over one-year. This suggests, remarkably, that rates of atrophy over one year provide information in regard to likelihood of future clinical diagnoses (and likely long-term outcome) in addition to that gained from a measure of functional change (CDR) over the same time period.

Studies of neuroimaging changes in preclinical AD vary greatly in terms of the subjects studied and the descriptive terms used for those subjects. Some groups define 'preclinical' based on a CDR of 0.5, termed 'questionable AD'. Subjects in this category most often contain both aMCI and SNCI subjects (Killiany et al. 2000;Killiany et al. 2002). Other groups have relied upon the conversion of normal controls to diagnosis of aMCI or AD (Carmichael et al. 2007;Jack, Jr. et al. 2004;Jack, Jr. et al. 2005;Jack et al. 2000;Rusinek et al. 2003). Often in these studies, little indication was given as to whether these subjects self-referred regarding memory complaints, or whether they were simply recruited for 'healthy aging' studies from the community. Still others have made group comparisons between MCI and 'cognitive complaints' groups, without looking at the differences between converters and non-converters (Saykin et al. 2006). Differing cohort composition makes direct comparison of our SNCI group with other 'cognitively normal' or 'non-demented' groups at baseline more

difficult, as it does comparison of the clinical application of their findings. Despite this, our rates of whole brain and hippocampal atrophy in the SNCI converters are similar to those of several of these studies, suggesting that there is some comparability (Jack et al. 2000;Rusinek et al. 2003).

The central hypothesis of this study was that rates of change measured by serial MRI would be predictive of future cognitive decline. Our results suggest that this is the case and importantly that rates of atrophy add predictive information over and above the change in clinical rating scores. These findings suggest that there is value in carrying out serial MRI scans to identify which patients with symptoms of memory loss will decline clinically, at least over 2 years.

10.6.3 MCI

10.6.3.1 Analysis 1

There was no evidence of a relationship between rates of whole brain, ventricular or hippocampal change and either outcome 1 or outcome 2 in the MCI group.

Table 10-17 Rates of change in the MCI converters and non-converters.

	Whole brain atrophy %volume/y		Ventricular enlargement ml/y		Total Hippocampal atrophy %volume/y	
Group	Non-converter	Converter	Non-converter	Converter	Non-converter	Converter
Rate	0.9 (0.8)	1.5 (0.5)	3.0 (2.7)	4.1 (1.5)	2.3 (1.6)	4.8 (3.0)

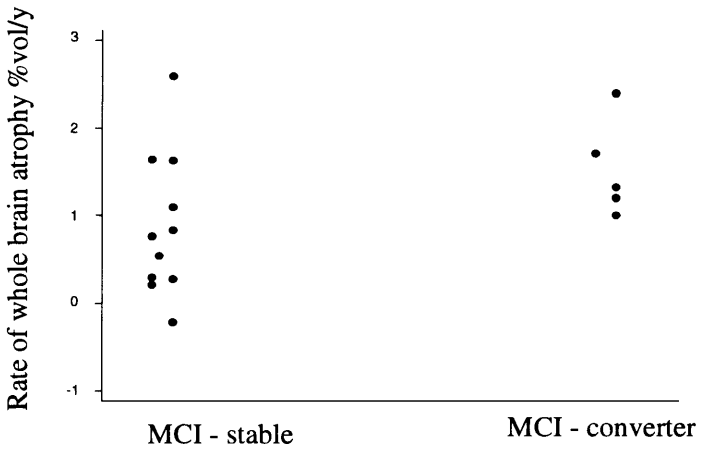


Figure 10-22 Relationship between rate of whole brain atrophy over one year and clinical diagnosis at two years in the MCI group

10.6.3.2 Analysis 2

There was no evidence of a relationship between baseline whole brain, ventricular or hippocampal volume and either clinical outcome or sum of boxes at 2 years.

There was no statistically significant relationship between whole brain or ventricular volume at one year and either outcome 1 or outcome 2.

There was a statistically significant relationship between baseline CDR and the sum of boxes at 2 years (p=0.001). After adjustment each unit increase in the sum of boxes at baseline was associated with an increase of 1.11 (95% CI 0.53-1.7) in the sum of boxes at 2 years. There was no evidence of a relationship between baseline sum of boxes and clinical diagnosis at 2 years.

There was no evidence of a relationship between the sum of boxes at one year and outcome 1 or 2 (adjusting for baseline sum of boxes).

10.6.3.3 Summary MCI

Within the MCI group, only the baseline and one-year sum of boxes were statistically significantly associated with sum of boxes at 2 years. Although rates of whole brain and hippocampal atrophy were generally higher in the converters than in the MCI non-converters, there was no evidence that increased rates of change, or baseline or one-year volumes, in the MCI group were associated with a diagnosis of AD at 2 years.

10.6.3.4 Discussion MCI

In the MCI cohort, there was no relationship between cross-sectional volumetric measures, or rates of whole brain, hippocampal or ventricular change and outcome at 2 years. This finding was initially unexpected as the literature available suggested a relationship between baseline hippocampal volume and progression to AD (Devanand et al. 2007;Jack, Jr. et al. 2005;Jack et al. 1999;Tapiola et al. 2006;Visser et al. 2002) and rates of whole brain (Jack, Jr. et al. 2004;Jack, Jr. et al. 2005) and hippocampal (Jack, Jr. et al. 2004;Jack et al. 2000) and ventricular change (Jack, Jr. et al. 2005) and clinical progression. Although controversy exists as to which rates of change are more predictive than others (e.g., rates of hippocampal or entorhinal cortex change (Stoub et al. 2005) and whole brain or ventricular change (Jack, Jr. et al. 2005)) some studies, like ours, have been able to differentiate between AD, MCI and control groups using hippocampal or entorhinal cortex rates of atrophy, but have not been able to use these measures to differentiate MCI converters from non-converters (Killiany et al 2002).

The inability to differentiate between MCI converters and non-converters in this study may have resulted from two factors. First, although rates of whole brain and hippocampal atrophy were higher in the MCI converters than in the non-converters, comparisons between the two groups failed to reach significance. This could be due in part to small study numbers: our neuroimaging measures may have differentiated converters from non-converters in a larger cohort. Second, subgroup differentiation may have been limited by our pre-selected study end-point of 2 years. Most studies which have shown that neuroimaging measures are predictive of future cognitive decline have had longer periods of follow up, typically up to 5 years with scan intervals of up to 2 years, and no fixed end-points (Devanand et al. 2007;Fleisher et al. 2005;Jack et al. 1999;Jack, Jr. et al. 2004;Stoub et al. 2005). It is likely that with a further year of follow-up in this study, the number of MCI converters and non-converters will have

changed. Further analysis of this cohort in future years should resolve this conundrum. Despite this, reassessing all study participants two years after study entry has clinical relevance, as often review occurs in a clinical setting on a yearly basis.

Characterisation of MCI cohorts has been as difficult in neuroimaging studies as in clinical and neuropsychological ones. Standardising cognitive status and coexisting disease processes (e.g., vascular disease or psychiatric disorders) has been problematic with the result that cognitive ability has varied widely between different MCI groups. Interestingly, where hippocampal atrophy rates have been found to relate to outcome, MMSE scores are often as low as 24 and can be as low as 18 (Jack, Jr. et al. 2004). Where a relationship has not been found, baseline cognitive scores within the MCI group have tended to be higher (average MMSE >26)(Jack, Jr. et al. 2005;Stoub et al. 2005). Other studies have found relationships with neuroimaging where outcome measures have been widened to include individuals who have shown cognitive decline but no evidence of dementia (Visser et al. 2002).

A range of conversion rates from MCI to AD have also been found. Some population and clinical studies have reported rates as low as 7% (Devanand et al. 2007;Tapiola et al. 2006), whilst in this study the conversion rate to AD was 15% per year.

A wide variation in the stages of the disease process, as well as in the underlying disease processes themselves, increases the likelihood of differentiation of MCI converters (AD pathology of a certain stage in progression) from MCI non-converters (mix of pathologies and varying stages in disease progression). The MCI cohort in this study was easily differentiated from the control and SNCI cohorts, with rates of atrophy that were consistent with early AD. Careful neuropsychological assessment and MMSE and CDR testing, suggested functional status consistent with MCI, with a similar cognitive status level in each case. Our high conversion rate and rates of cerebral change suggest the presence of an underlying neurodegenerative disease, likely in the majority of patients to be due to AD. This homogeneity in underlying pathology may increase the difficulty in distinguishing those at increased risk of AD as almost all are at risk of AD.

Finally, where relationships between neuroimaging and outcome have not been found in other studies, technical considerations, such as the degree of automation involved in

outlining and measuring brain regions, have been suggested as possible reasons (Jack, Jr. et al. 2005). In this cohort intra- and inter-rater reproducibility was high for all measurements, and most processes were at least semi-automated.

Although a relationship between the measures of neuroimaging and the clinical progression of the disease was not found at the end point of this particular study, further follow-up of this cohort (ongoing) will be valuable to determine whether and at what point differentiation of the converters from non-converters will become possible.

11 Longitudinal neuropsychological analysis

11.1 Introduction

All subjects had a full neuropsychological assessment at entry to the study and one year later, as described in chapter 6. In this chapter we relate how performance on these tests differed over a one-year period for the control, MCI and SNCI groups. We also compare the performance of those SNCI and MCI subjects who converted to a diagnosis of MCI or AD after a two-year period to those of the non-converters in each of their respective cohorts.

11.2 Methods

11.2.1 Statistical analysis

11.2.1.1 Floor and ceiling effects

Neuropsychological tests are not always able to measure the entire distribution of a given activity. Ceiling effects refer to where a test is of insufficient difficulty to allow differentiation of patients attaining the highest score. For example in the MMSE, individuals performing both at normal and high levels of functioning should attain scores of 30 out of a total of 30.

A floor effect is found where a test is particularly difficult for a group of subjects, so that everyone scores at the lowest level despite having a range of ability. In the MCI group there was a floor effect on tests of memory (eg: Recognition memory test for words and faces), where many subjects scored at the lowest level although they may have had different recall abilities. It is important to take these floor and ceiling effects into account in the analysis of the longitudinal data because where a subject has scored the highest possible or lowest possible scaled score on a given test we may not be able to accurately measure change in their cognitive performance.

11.2.1.2 Accounting for floor and ceiling effects

In this thesis, we addressed the difficulties of carrying out longitudinal analysis where data are censored due to floor and ceiling effects by utilising a form of interval regression based on Tobit regression (StataCorp 2003). This regression assumes that data are truncated, or censored, above or below certain values (e.g., by floor or ceiling effects). Where there are values at ceiling, the assumption is made that these values will be normally distributed. Maximum likelihood is then used to estimate score parameters. In turn the mean score is then altered to reflect these new values. This method was used as an experimental approach within this thesis, with the aim of making improved estimates of our groups' change in neuropsychological performance where there was right or left censoring (floor and ceiling effects) of data.

In practice change in neuropsychological performance was determined by carrying out interval regression on the follow-up neuropsychological scores (outcome variable), where it was specified whether scores were at floor or ceiling. Subject group was a predictor variable. Floor and ceiling effects in baseline scores were dealt with by adding baseline scores and a dummy variable (indicating whether scores were at floor or ceiling) into this multivariable regression model. Where neuropsychological scores had not already been adjusted for age and education (through scaling or grading of scores), these were added in as additional covariates. Robust standard errors were used in these models to allow for the differential heterogeneity between our three study groups.

Interval regression was also used to assess the relationship between change in neuropsychological performance and outcomes 1 and 2. Although logistic regression is the natural approach when outcome is binary, a marked difference between the P-values for the Wald and likelihood ratio tests in this dataset suggested that the logistic regression models should not be relied on.

This secondary analysis (relationship between change in performance and outcome) treated change in clinical diagnosis and sum of boxes at 2 years as predictors of change in neuropsychological score. The MCI and SNCI data were analysed separately.

Recognition of possible floor and ceiling effects in the analysis of our data, allowed for the fact that scores in our groups were artificially curtailed, and permitted the possibility

of change in subject performance where scores were at floor or ceiling level on both baseline and follow-up. This may not have been discernible using other techniques.

Some limitations to this technique however, must be borne in mind when interpreting this data. First, this regression assumes that if right or left censoring were not in operation then the scores at ceiling would fall into a normal distribution. This may not always be the case. Second, where almost all scores are at ceiling (e.g., control performance on the MMSE) or at floor, the distribution of scores achieved by using Tobit regression may result in derivation of a mean score that is driven by untestable assumptions. For this reason, mainly p-values but not confidence intervals or effect estimates are reported.

11.2.1.2.1 Cross-sectional analysis

To assess the relationship between baseline scores and both outcomes within the MCI and SNCI group, regression analysis was carried out where baseline score was the dependant variable and outcome the predictor variable. Years of education and age were added as covariates where this was not taken into account in the scaling of scores.

Similarly to the baseline analysis, if English was spoken as a foreign language, individuals were removed from the analysis where this may have had a confounding effect on any associations seen (see section 7.3.1).

In all of these analyses, it was decided not to make Bonferroni-type corrections for multiplicity. This decision is controversial, although a number of authors (e.g., Perneger et al 1998 (Perneger 1998), Rothman et al 1990 (Rothman 1990), Savitz and Olshan 1995 (Savitz and Olshan 1995) and Thompson et al 1998 (Thompson 1998) have argued against their use . Our view is that they should only be used when the associations being investigated are so 'similar' that they are not of independent scientific interest. This was not believed to be the case in this study.

11.2.2 Longitudinal neuropsychology results

11.2.3 Group comparisons and change over one year

11.2.3.1 SNCI

The mean annual change in neuropsychological performance was similar in the SNCI group and controls. Only change in performance on the CVLT delayed recall was significantly different, with the SNCI improving more than the controls.

11.2.3.2 MCI

Overall the MCI group, showed a decrease in performance on many tests of memory (CVLT delayed recognition, RMT words and faces), a test of global cognition (MMSE), naming (GNT) and executive function (part A and B of the Trail Making Test). By contrast, performance on measures of IQ (NARTIQ and WASIFSIQ) remained stable.

Compared with the control group, the MCI had a significantly greater decrease in neuropsychological performance on the RMT words and faces, the MMSE and the GNT. Compared to the SNCI the MCIs showed a significantly greater decrease in score on the RMT words and faces and MMSE.

Table 11-1 Baseline, follow-up and annual change in scores for each group

Mean scores are given with standard deviations in brackets*. P-values are given for between group comparisons adjusted for floor and ceiling effects. N refers to the number of subjects who took this test at baseline and follow up, where this is not the full cohort. B/L = baseline, 1 = one year and D = change over one year. Scores are scaled unless otherwise indicated.

Variable	Controls			SNCI			MCI			Between group comparisons		
	B/L	1	D	B/L	1	D	B/L	1	D	M v C	S v C	M v S
MMSE	29.8 (0.5)	29.7 (0.5)	**-0.1 (0.5)**	29.4 (0.9)	29.2 (1.1)	**-0.2 (1.3)**	27.7 (1.4)	26.9 (2.8)	**-0.8 (2.9)**	**<0.001**	0.07	**0.02**
NARTIQ * n=28/21/26	114 (11)	115 (10)	**1.1 (3.4)**	112 (13)	114 (12)	**1.7 (3.7)**	105 (18)	106 (16)	**1.1 (3.9)**	0.33	0.07	0.35
WASI vocab n=28/21/26	13.3 (2.3)	14.6 (1.8)	**1.4 (1.4)**	13.4 (2.4)	14.3 (1.7)	**0.9 (1.3)**	11.3 (3.4)	12.3 (2.2)	**1.0 (2.0)**	**0.001**	0.21	**0.02**
WASI Matrices	13.3 (2.6)	13.0 (2.7)	**-0.3 (2.3)**	11.9 (2.5)	12.0 (2.5)	**0.1 (1.9)**	12.0 (2.8)	11.3 (3.0)	**-0.6 (2.3)**	0.24	0.87	0.23
WASI FSIQ * n=28/21/26	120 (13)	123 (12)	**3.4 (8.9)**	117 (12)	119 (11)	**1.7 (7.7)**	110 (14)	111 (13)	**0.2 (9.5)**	**0.01**	0.26	0.06
CVLT Immediate Recall	13.5 (1.9)	14.1 (1.9)	**0.6 (2.4)**	12.3 (2.7)	12.6 (2.8)	**0.3 (1.9)**	7.2 (3.4)	8.2 (4.2)	**1.0 (2.2)**	0.28	0.17	0.79
CVLT Delayed Recall	14.3 (2.0)	14.6 (2.0)	**0.3 (2.1)**	12.5 (2.1)	13.2 (3.0)	**0.8 (2.3)**	7.0 (4.2)	7.1 (3.8)	**0.1 (2.5)**	**0.04**	0.97	**0.02**
CVLT Delayed Recognition	13.5 (1.2)	13.0 (1.4)	**-0.5 (1.3)**	13.0 (1.6)	13.2 (2.3)	**0.2 (2.2)**	7.1 (3.7)	6.8 (4.3)	**-0.2 (2.8)**	0.75	**0.02**	0.17
RMT Words	13.2 (1.7)	13.3 (1.6)	**0.1 (1.2)**	12.6 (2.3)	12.3 (2.8)	**-0.3 (1.8)**	6.6 (2.4)	5.9 (2.5)	**-0.7 (3.0)**	**0.002**	0.53	**0.005**
RMT Faces	11.6 (3.2)	12.8 (2.6)	**1.0 (3.1)**	12.8 (2.9)	12.9 (3.3)	**0.1 (2.3)**	6.7 (3.7)	6.5 (3.1)	**-0.2 (3.6)**	**<0.001**	0.88	**<0.001**
ROF * Immed. Recall N=26/20/28	3.9 (1.6)	4.4 (1.2)	**0.5 (1.5)**	2.9 (1.8)	3.5 (1.6)	**0.5 (1.5)**	1.1 (1.5)	1.3 (1.5)	**0.2 (1.0)**	**0.01**	0.30	0.06
ROF* Delay Recall N=26/20/28	3.9 (1.5)	4.2 (1.5)	**0.4 (1.5)**	2.7 (2.1)	3.2 (1.8)	**0.5 (1.7)**	0.5 (1.1)	0.9 (1.5)	**0.4 (0.6)**	**0.02**	0.11	0.13
GNT * n=28/21/26	12.9 (2.9)	13.5 (2.8)	**0.6 (1.7)**	12.3 (3.6)	12.5 (3.2)	**0.2 (1.2)**	10.2 (3.2)	9.8 (3.7)	**-0.4 (2.1)**	**0.03**	0.31	0.12
VOSP Silhouettes	9.5 (2.6)	9.8 (2.9)	**0.4 (2.0)**	9.0 (2.9)	9.0 (3.1)	**0.0 (2.5)**	8.3 (2.8)	8.9 (2.4)	**0.6 (2.3)**	0.91	0.40	0.51
Trails A	10.3 (2.9)	9.8 (2.8)	**-0.5 (2.4)**	9.3 (2.9)	9.1 (3.0)	**-0.2 (2.3)**	8.9 (3.1)	8.5 (3.7)	**-0.4 (3.6)**	0.64	0.96	0.67
Trails B	11.5 (2.3)	11.0 (3.1)	**-0.5 (2.3)**	9.7 (3.6)	9.9 (3.9)	**0.2 (2.1)**	8.6 (2.7)	8.3 (3.0)	**-0.3 (1.9)**	0.89	0.38	0.27
Trails Difference	38.9 (20)	42.1 (26)	**3.2 (25)**	66.6 (54)	62.1 (55)	**-4.5 (35)**	77.4 (51)	79.7 (60)	**2.2 (32)**	0.57	0.60	0.37

*** ROF scores were graded, and NART and WASI IQ were scored using an IQ scale. Trails difference is the subtraction of Part A from Part B of the TMT (seconds), a negative change indicates an improvement in performance.**

11.2.4 Association between change in neuropsychological performance over one year and outcome at 2 years

11.2.4.1 SNCI

Compared with the SNCI non-converters, over one year the SNCI converters experienced either a decrease in performance or less of an improvement in performance on the majority of tests in the neuropsychological battery.

Our analysis in this group has been necessarily limited by the small number of subjects that converted to a diagnosis of MCI or AD, although this has allowed us to examine each of their neuropsychological performances in detail over the follow-up period.

Table 11-2 Mean baseline, follow-up and annual change in scores for the SNCI converters and non-converters

	SNCI converters N=4			SNCI non-converters N=31		
	B/L	1	D	B/L	1	D
MMSE (not scaled)	29.3 (1.0)	28.3 (2.2)	-1 (2.8)	29.5 (0.9)	29.4 (0.9)	-0.1 (1.0)
NARTIQ (IQ scale) (4/22)	118 (3.6)	118.3 (4.7)	0.3 (3.6)	110.9 (14.0)	112.9 (13)	2.0 (3.7)
Wasi Vocab (4/22)	14.8 (1.3)	15 (0.8)	0.3 (1.0)	13.2 (2.5)	14.2 (1.8)	1.0 (1.3)
WASI Matrices	10.8 (3.0)	11.3 (4.7)	0.5 (2.4)	12.0 (2.5)	12.1 (2.2)	0.1 (1.9)
FSIQ (IQ scale) (4/22)	115.8 (11.6)	119.8 (16.5)	4 (8.4)	117.6 (12.6)	118.9 (10)	1.3 (7.7)
CVLT Immediate recall	10 (3.6)	9 (3.4)	-1 (1.4)	12.6 (2.5)	13.0 (2.4)	0.4 (1.9)
CVLT Delayed recall	10.3 (2.2)	9 (4.2)	-1.3 (2.4)	12.7 (2.0)	13.8 (2.4)	1.0 (2.2)
CVLT Recognition	11.3 (2.8)	9 (4.8)	-2.3 (5.6)	13.2 (1.3)	13.7 (0.9)	0.5 (1.3)
RMTW	11.3 (3.3)	9 (4.9)	-2.3 (2.6)	12.8 (2.2)	12.8 (2.1)	0.0 (1.6)
RMTF	11.0 (3.7)	8.5 (3.3)	-2.5 (2.5)	13 (2.7)	13.5 (2.9)	0.5 (2.0)
ROF Immed. Recall (Graded) (4/22)	1.8 (1.5)	2.0 (0.8)	0.3 (1.7)	3.1 (1.8)	3.7 (1.6)	0.6 (1.5)
ROF Delayed Recall (Graded) (4/22)	0.8 (0.5)	1.0 (0.8)	0.3 (1.0)	3.0 (2.1)	3.6 (1.6)	0.5 (1.8)
GNT (4/22)	12.8 (3.3)	13.0 (3.6)	0.3 (0.5)	12.2 (3.7)	12.4 (3.2)	0.2 (1.3)
VOSP	9.5 (3.3)	7.3 (1.7)	-2.3 (4.0)	8.9 (2.9)	9.2 (3.2)	0.3 (2.2)
TrailsA	9.0 (2.5)	7.6 (3.8)	-1.4 (2.8)	9.4 (3.0)	9.3 (2.9)	0.0 (2.3)
TrailsB	8.2 (4.2)	8.9 (5.2)	0.7 (1.7)	9.9 (3.6)	10.1 (3.8)	0.2 (2.2)
Trails difference (not scaled)	95.8 (93.0)	79.5 (89.7)	16.3 (7.6)	62.8 (48.0)	59.8 (50.3)	3 (36.9)

11.2.4.1.1 Individual analysis

Converter 1

This individual demonstrated a relative weakness in verbal memory at baseline. This became even more pronounced at one year when a marked discrepancy became discernible between the verbal and visual memory components of the RMT (significant discrepancy defined as visual memory score more than 4 points greater than verbal score, or verbal score more than 7 points greater than visual score (Warrington 1984)). With the exception of this isolated memory deficit, at two years the other cognitive domains were relatively well preserved.

Converter 2

This subject also had the suggestion of an early verbal memory deficit at baseline, particularly in comparison with their visual memory performance on the RMT. Verbal memory became impaired according to study criteria by one year on the RMT for words, progressing to affect the CVLT at two years. In this individual there was also a suggestion that by the 2nd follow up visit, naming was beginning to be affected.

Converter 3

Although this subject performed within the normal range at baseline on memory tests, a selective visual memory weakness was again highlighted by the difference between the scores on the verbal and visual versions of the RMT. Despite this, the performance was not judged to be impaired until the third assessment. In addition, the progressively worsening performance on the GNT should be noted, suggesting involvement of naming.

Converter 4

Although not impaired on memory at baseline, again evidence was apparent of early memory difficulties, with worse performance seen on the visual than verbal component of the RMT. At one year, memory performance became impaired, and there was also evidence of involvement of reasoning and executive functioning. This subject became

impaired on the WASI matrices and experienced difficulties on the TMT, which extended from part B to the easier part A. By the third visit this individual had a clinical diagnosis of AD.

Table 11-3 Individual raw scores for the SNCI converters

Scores are given at baseline (0) and after one year (1) and two years (2) of follow up, scaled scores in italics. Scaling of scores is as in previous tables. A score in bold reflects a performance less than 1.5 standard deviations from the mean

	Converter 1			**Converter 2**			**Converter 3**			**Converter 4**		
	0	**1**	**2**	**0**	**1**	**2**	**0**	**1**	**2**	**0**	**1**	**2**
MMSE	28	29	28	30	29	29	29	30	29	30	25	29
WASI	71	74	75	75	73	75	75	77	74	66	70	74
vocab	*15*	*15*	*16*	*16*	*15*	*16*	*15*	*16*	*16*	*13*	*14*	*15*
WASI	22	26	25	21	19	22	18	25	22	9	**6**	10
Matrices	*14*	*16*	*15*	*12*	*11*	*13*	*10*	*13*	*13*	*7*	***5***	*7*
WASI	124	137	133	123	118	125	117	126	119	99	98	108
FSIQ												
NARTIQ	115	120	117	120	118	115	122	123	123	115	112	110
CVLT	19	21	23	30	25	**16**	34	33	28	19	**15**	**16**
I. Recall	*7*	*8*	*9*	*12*	*10*	***5***	*14*	*13*	*10*	*7*	***5***	***5***
CVLT	6	**2**	**2**	12	11	**3**	15	18	12	12	7	8
D. Recall	*7*	***4***	***4***	*11*	*10*	***5***	*12*	*14*	*10*	*11*	*8*	*9*
CVLT	32	28	29	30	34	32	36	36	35	35	**24**	29
D. Recog	*10*	*6*	*7*	*8*	*12*	*10*	*14*	*14*	*13*	*13*	***4***	*7*
RMTW	44	**34**	38	38	**35**	**34**	49	50	46	46	44	37
	11	***5***	*7*	*7*	***5***	***5***	*15*	*15*	*12*	*12*	*11*	*6*
RMTF	47	46	45	44	36	38	43	42	**35**	36	36	34
	15	*13*	*12*	*12*	*6*	*7*	*11*	*9*	***5***	*6*	*6*	*4*
ROF	8	12.	10	15.5	12.5	11	13	14	13	10.	9.5	9.5
I.Recall	*1*	*5 3*	*2*	*4*	*2*	*2*	*1*	*2*	*1*	*5*	*1*	*1*
ROF	**6**	6.5	7.5	10.6	11.5	**7.5**	12	14	12	9	**5**	N/A
D.Recall	***0***	*1*	*1*	*1*	*2*	***0***	*1*	*1*	*1*	*1*	***0***	
GNT	26	27	27	27	27	20	22	21	14	19	19	19
	15	*16*	*16*	*16*	*16*	*10*	*11*	*11*	*6*	*9*	*9*	*9*
VOSP	12	9	10	10	10	10	**7**	8	9	12	**6**	**7**
	12	*8*	*9*	*9*	*9*	*9*	***5***	*7*	*8*	*12*	***5***	***5***
Trails A	30	29	29	41	53	38	43	40	49	48	**87**	**66**
	12	*12*	*12*	*10*	*8*	*10*	*6*	*8*	*6*	*7*	***3***	***5***
Trails B	76	60	91	85	91	119	101	75	80	**283**	**301**	**301**
	12	*13*	*10*	*11*	*11*	*9*	*8*	*10*	*9*	***3***	***1***	***1***
Trails	46	31	62	44	38	81	58	35	31	235	214	235
Diference												

11.2.4.1.2 Group analysis

Having examined the individual neuropsychological performances in detail, analysis was next undertaken to assess whether mean change in performance over one year or mean baseline neuropsychological scores were significantly different between the SNCI converters and non-converters at 2 years.

Table 11-4 Significant associations between scores at one year on neuropsychological tests and conversion to MCI or AD at two years in the SNCI group

All analysis was adjusted for baseline score, floor and ceiling effects at follow up and baseline, and age and education where required.

Outcome	P-value	Difference in score at one year between the SNCI converters and non converters, whilst adjusting for baseline score	95% Confidence interval
CVLT immediate recall*	0.009	-2.3	-4.0, -0.6
CVLT delayed recall	0.023	-3.0	-5.6, -4.2
RMT faces	<0.001	-4.3	-6.3,-2.5
ROF Immediate Recall	0.043	-1.4	-2.8, -0.04

***After adjustment a diagnosis of MCI or AD at 2 years (SNCI converter = 1, SNCI non converter = 0) was associated with a decrease in scaled score of 2.3 points at one year on the CVLT immediate recall (95% CI –4.0, -0.6).**

Table 11-5 Association between baseline neuropsychological performance and clinical diagnosis of MCI or AD at two years in the SNCI group

Outcome	P-value	Difference in baseline score between the SNCI converters and non converters	95% Confidence interval
CVLT delayed recall*	0.028	-2.8	-5.3, - 0.3
CVLT delayed recognition	0.026	-3.5	-6.5, - 0.4
ROF delayed recall	0.008	-4.4	-7.7, - 1.1
VOSP	0.018	-3.4	-6.2, - 0.6

***After adjustment a diagnosis of MCI or AD at 2 years was associated with a scaled score of 2.8 points lower on the CVLT delayed recall in the SNCI converters than in the non-converters (95% CI –5.3, -0.3).**

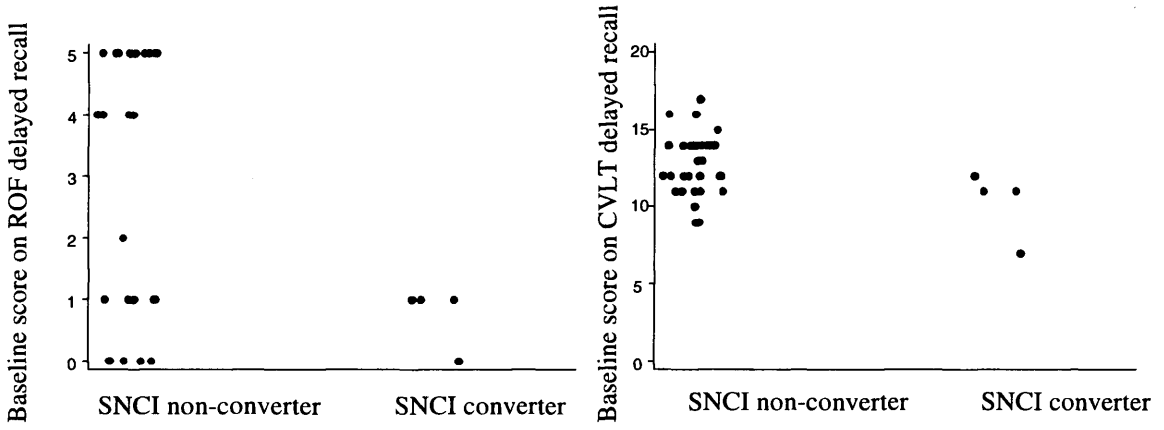


Figure 11-1 Relationship between baseline scores on the ROF and CVLT and clinical outcome at two years

Statistical comparisons of the converters and non-converters in the SNCI had to be carried out carefully due to the small numbers of converters. Several significant associations were found between baseline memory performance and changes in memory performance and both outcomes (see Tables 11-4 and 11-5); however, when these associations were related to the individual scores of the converters it was felt that they were not entirely representative of the converter group. For example, a relationship was found between poor baseline performance on the VOSP silhouettes subset and subsequent clinical decline. One SNCI converter was originally impaired in this test but subsequently went on to improve his performance throughout the course of the follow-up. One impaired individual in a group of this size may have had a substantial effect on this relationship.

Furthermore, where relationships were found between changes in neuropsychological performance and clinical outcome, it was felt that these differences relied upon the fact that the non-converters were able to improve their scores (via a practice effect) rather than that there had been an overall decrease in performance by the SNCI converters. For this reason, analysis in the SNCI between converters and non-converters and clinical outcome was limited to the above comparisons.

11.2.4.1.3. SNCI discussion

Overall as a group, performance on neuropsychological tests over one year was similar between the SNCI and control cohorts. This suggests that the SNCI do indeed form a heterogeneous group, with a small proportion converting to MCI or AD whose neuropsychological performances were overshadowed by the rest of the 'normal' group.

Clearly, however, a proportion of the SNCI group are at risk of developing neurodegenerative disease, and, indeed, four had done so by the 2nd year of the study. Almost all the converters showed a discrepancy between verbal and visual memory on the recognition memory test at baseline, despite not reaching the level for memory impairment required by our study criteria. This finding reinforces the necessity within a clinical setting of assessing each individual in turn and looking for relative weaknesses rather than absolute impairment within their neuropsychological profile. In the clinical setting the verbal/visual memory discrepancy would have identified these individuals as being worthy of follow-up in the presence of memory complaints. Early changes in episodic memory in these four converters are consistent with the changes expected in early AD. A drop in performance level on tests of episodic memory has been found to be an early indicator of incipient AD by a number of studies (Howieson et al. 2003;Jack et al. 2004). The relationship present in this study between poor baseline memory test performance and increased risk of AD has also been found by other groups (Blacker et al. 2007;Chen et al. 2000;Elias et al. 2000;Fox et al. 1998;Jacobs et al. 1995). Overall, the range of scores on tests of IQ and reasoning suggest that these converters were high-functioning individuals. Their requesting medical help for memory problems at a stage where memory was not clinically impaired suggests that these individuals had good insight into their difficulties. Interestingly, high-functioning individuals are recognised in the literature as representing a group still at potential risk of cognitive decline despite a lack of demonstrable cognitive impairment (Jonker et al. 2000). This is thought to be mainly due to many tests not being sensitive enough to detect impairment in memory at an early stage in the disease.

The small number of conversions to MCI or AD precluded extensive analysis to evaluate the neuropsychological risk factors for conversion in terms of baseline scores and change in neuropsychological performance. Unlike neuroimaging, which is

quantitative and uninfluenced by variables such as anxiety, depression or practice effects, each neuropsychological test has a number of specific attributes that can make it more stable to changes over time, or conversely more sensitive to a particular change. These attributes can be useful where tests are taken in isolation and an individual subject's performance is assessed, but can potentially make group comparisons more difficult, as was our experience. These difficulties may be overcome if a larger cohort of converters becomes available with the continued follow-up of this cohort. On review of the different neuropsychology scores, it was felt that in the converter group no one test was consistently affected at baseline and follow-up. Each subject became gradually impaired on different tests of memory and some not until the 2nd year of follow-up. On the whole, however, subjects' memory performance both at baseline and over the course of one year was identified as a marker of future conversion to MCI /AD, which would be consistent with a 'pre AD' group.

Interestingly, where differences existed between change in neuropsychological performance over one year and clinical outcome at 2 years, this seemed to be mainly driven by practice effects. Practice effects are distinct from day-to-day fluctuations in performance and refer to the bias introduced at the second test session due to familiarity with the test procedure and also specific test items. Factors that increase the likelihood of a practice effect are a speeded component, with an infrequently practised response, or with an easily conceptualised solution. For certain tests these effects may also depend on IQ score, with greater effects associated with higher IQs. Certain tests such as the GNT have small practice effects with a mean gain in scores of approximately one word with testing after an interval (Bird et al. 2004;Bird et al. 2004), whilst other tests, particularly memory tests may have larger effects (e.g. the Recognition Memory Test). Galvin et al (Galvin et al. 2005) found that in their older cohort of non-symptomatic community dwelling subjects, a neuropathological diagnosis of AD was associated with a lack of improvement with repeated testing in a test of naming, and suggested that the absence of practice effects on certain cognitive measures might indicate those individuals without dementia who have underlying neuropathologic AD. Lack of practice effects in tests of verbal recall have also been proposed as distinguishing between those at risk of AD and normal controls (Caselli et al. 2004). In this study it was thought that although a practice effect might be the inevitable result in 'normal' individuals of improving performance due to familiarity, this effect is not always predictable nor always seen in normal individuals. Therefore, an observable practice

effect was not thought to represent a good discriminator between SNCI converters and non-converters, but more likely a potential study confounder.

Finally, when assessing an individual's change in scores over time, it is also important to know how much of a change in scores is significant. Bird et al (Bird et al. 2003) found that a significant improvement or decline in performance on the RMT words was associated with a change in score of one to two percentile bands. For the non-verbal subtest a score improvement was associated with a rise by two to four bands whilst a drop was associated with a change of one to two bands. Should change in neuropsychological performance be used to predict outcome, it would be necessary to know how much of a change is required to demonstrate an actual change in cognitive performance.

11.2.4.2 MCI

11.2.4.2.1 Change in neuropsychology and clinical diagnosis at 2 years

Table 11-6 Mean baseline, follow-up and annual change in scores in the MCI non-converters and converters

All scores are scaled unless otherwise indicated (standard deviations in brackets)

	MCI Non Converters N=14			MCI converters N=6		
	B/L	1	D	B/L	1	D
MMSE	27.71 (1.4)	28 (2)	0.29 (2.1)	27.67 (1.5)	25 (3.0)	-2.67 (3.4)
WASI vocab	10.36 (3.5)	11.86 (2.2)	1.5 (2.2)	13.33 (2.3)	13.3 (2.3)	0 (0.6)
WASI Matrices	12.5 (2.3)	11.79 (2.7)	-0.71 (2.5)	10.5 (3.62)	10.17 (3.9)	-0.33 (2.3)
WASI FSIQ (IQ points)	108.79 (15.2)	110.21 (12.1)	1.43 (10.4)	112.5 (13.0)	111.17 (17.1)	-1.33 (7.4)
NARTIQ (IQ points)	106.43 (17.8)	106.86 (15.6)	0.43 (3.9)	99.33 (19.6)	101 (18.6)	1.67 (3.7)
CVLT Immediate Recall	7.86 (3.8)	9.36 (4.3)	1.5 (2.0)	6.17 (2.1)	6.17 (3.4)	0 (2.6)
CVLT Delayed Recall	7.07 (4.8)	7.64 (4.5)	0.57 (2.6)	6 (2.2)	6 (1.8)	0 (1.4)
CVLT Delay Recognition	7.86 (3.1)	8.14 (4.3)	0.29 (2.8)	4.7 (4.3)	4 (3.0)	-0.67 (2.1)
RMT Words	6.43 (2.4)	6.14 (2.8)	-0.29 (3.1)	6.83 (2.9)	5.67 (1.6)	-1.17 (3.1)
RMT Faces	5.64 (2.6)	6.57 (3.2)	0.93 (3.3)	9 (5.3)	6.67 (3.3)	-2.3 (3.4)
ROF Immediate Recall (Graded) (13/6)	1.38 (1.7)	1.62 (1.8)	0.23 (1.1)	0.67 (0.8)	0.5 (0.55)	-0.17 (0.8)
ROF Delayed Recall (Graded)	0.69 (1.3)	1.14 (1.7)	0.54 (0.7)	0.17 (0.4)	0.17 (0.4)	0 (0)
GNT	10 (3.5)	10.14 (4.4)	0.14 (2.1)	11.17 (2.5)	9 (1.9)	-2.17 (0.8)
VOSP	8.36 (2.8)	9 (2.1)	0.64 (2.7)	8.17 (3.3)	8.83 (3.3)	0.67 (1.4)
Trails A	8.5 (1.7)	9.06 (3.3)	0.56 (3.6)	8 (2.6)	5.95 (2.7)	-2.05 (3.4)
Trails B	9.01 (2.1)	8.86 (2.9)	-0.15 (2.3)	6.65 (1.9)	6.25 (1.7)	-0.4 (0.6)
Trails Difference (seconds)	63.71 (48.6)	72.43 (66.8)	8.7 (34.3)	114.83 (45.0)	102.17 (44.7)	-12.67 (26.6)

Table 11-7 Raw scores and scaled scores for the six MCI subjects who converted to a diagnosis of AD at two years

Scaled scores are in brackets, 0 = baseline, 1 = first year follow-up, 2 = second year follow-up

		MMSE	WASI	WASI	WASI	NARTIQ	CVLT	CVLT	CVLT	RMTF
MCI converter 1	0	28	57 (11)	15 (9)	98	81	19 (6)	5 (7)	**27 (5)**	**32 (4)**
	1	20	57 (11)	17 (10)	100	90	**9 (2)**	5 (7)	**20 (2)**	**33 (4)**
	2	23	59 (11)	7 (10)	101	84	**14 (4)**	**2 (4)**	**19 (2)**	**28(4)**
MCI converter 2	0	26	74 (15)	19 (10)	115	122	**15 (3)**	**4 (5)**	**24(4)**	48(16)
	1	23	75 (15)	13 (7)	106	124	**17 (4)**	**4 (5)**	**23 (3)**	38 (7)
	2	23	74 (15)	**8 (5)**	99	124	22 (7)	**1 (3)**	**17 (2)**	**26(4)**
MCI converter 3	0	28	72 (15)	21 (12)	118	108	24 (9)	6 (7)	**20 (2)**	46(13)
	1	27	75 (15)	25 (14)	127	107	24 (9)	4 (6)	**18 (2)**	45(12)
	2	22	73 (15)	15 (9)	112	105	22 (7)	**2 (4)**	**21 (3)**	39 (8)
MCI converter 4	0	26	74 (15)	12 (8)	112	113	17 (6)	**0 (2)**	**14 (1)**	**33 (4)**
	1	27	69 (14)	17 (10)	112	113	**14 (4)**	**2 (4)**	**22 (3)**	**31(4)**
	2	20	72 (15)	13 (9)	109	115	**11(3)**	**2 (4)**	**16 (2)**	**33(4)**
MCI converter 5	0	30	66(14)	26 (17)	133	101	18 (8)	6 (8)	34 (13)	**35 (5)**
	1	25	71 (15)	22 (15)	134	101	26 (11)	7 (9)	31 (10)	**27 (4)**
	2	26	68 (14)	23 (16)	130	108	25 (11)	4 (7)	30 (9)	**32 (4)**
MCI converter 6	0	28	54 (10)	12 (7)	99	71	**17 (5)**	5 (7)	**21 (3)**	45 (12)
	1	28	56 (10)	**7 (5)**	88	71	21 (7)	**3 (5)**	**24 (4)**	42 (9)
	2	26	54 (10)	10 (6)	89	86	**17 (5)**	**3 (5)**	**21 (3)**	49 (16)

		RMTW	ROF	ROF	GNT	VOSP	Trails A	Trails B	Trails Diff
MCI converter 1	0	**26(4)**	12(1)	11.5 (1)	20 (10)	11 (11)	57 (7)	218(6)	161
	1	**33(4)**	**8.5 (0)**	12 (1)	17 (8)	12 (12)	47 (8)	200(6)	153
	2	**30(4)**	**5 (0)**	**4 (0)**	15 (6)	11 (11)	52 (7)	**301(2)**	249
MCI converter 2	0	38(7)	**0.5 (0)**	**0 (0)**	23 (12)	**5 (5)**	39 (7)	**213(3)**	174
	1	**30(4)**	**4 (0)**	**0 (0)**	19 (9)	**6 (5)**	**79 (2)**	**228(3)**	149
	2	**31(4)**	**3.5 (0)**	**2 (0)**	23 (12)	**5 (5)**	**90 (2)**	**301 (0)**	291
MCI converter 3	0	**32(4)**	9 (1)	**5.5 (0)**	24 (13)	13 (13)	52 (6)	112(8)	60
	1	39(8)	10 (1)	**8 (0)**	21 (11)	12 (12)	42 (8)	137 (7)	95
	2	**29(4)**	11 (1)	**5 (0)**	19 (9)	12 (12)	45 (8)	**195 (5)**	150
MCI converter 4	0	38 (7)	**2.5 (0)**	**0 (0)**	25 (14)	8 (7)	63 (6)	141(8)	78
	1	36(6)	7.5 (1)	**3 (0)**	22 (11)	9 (8)	**118 (3)**	151(8)	33
	2	**34(5)**	9 (2)	**7 (0)**	22 (11)	9 (8)	63 (6)	152 (8)	89
MCI converter 5	0	46(12)	**7 (0)**	**2 (0)**	16 (7)	**6 (5)**	27 (13)	130(8)	103
	1	38(7)	5 (1)	**3.5 (0)**	15 (6)	**7 (5)**	50 (7)	133 (6)	83
	2	40 (8)	4 (1)	4 (1)	**12 (4)**	9 (8)	51 (7)	144 (6)	93
MCI converter 6	0	38 (7)	**3 (0)**	**1.5 (0)**	21 (11)	9 (8)	55 (8)	168 (7)	113
	1	**35 (5)**	**3 (0)**	**7.5 (0)**	19 (9)	11 (11)	54 (8)	154 (7)	100
	2	**26 (4)**	**1.5 (0)**	**2 (0)**	20 (10)	9 (8)	55 (8)	**293 (4)**	238

There was evidence of an association between a decrease in performance on the RMT faces, GNT and TMT Part A, and a diagnosis of AD at 2 years (see Table 11-8). Evidence of a relationship was also demonstrated between a decrease in performance on the ROF and clinical diagnosis at 2 years. It was felt, however, that this decline most likely represented a relative improvement of scores in a small proportion of subjects within the non-converter group, whilst due to the relative insensitivity of the grading within this test, the majority of MCI were at floor on both attempts as might be expected for a demanding test of memory and visuospatial function.

Table 11-8 Significant associations between neuropsychological tests at one year and whether a MCI subject had a clinical diagnosis of AD at two years.

All analysis was adjusted for baseline scores and floor and ceiling effects at follow-up and age and education where required.

Neuropsychological test	Difference in scaled score at one year between converters and non converters, whilst adjusting for baseline score	95%Confidence Interval	P-value
RMT faces*	-3.6	-6.7, -0.6	0.018
ROF delayed recall	-7.1	-9.0, -5.3	<0.001
GNT	-2.2	-3.7, -0.7	0.004
Trail making test Part A	-3.0	-6.0, -0.1	0.045

*** After adjustment a diagnosis of AD at 2 years was associated with a decrease in performance on the RMT faces at one year of 3.6 points (scaled score) (95% CI –6.7, -0.6).**

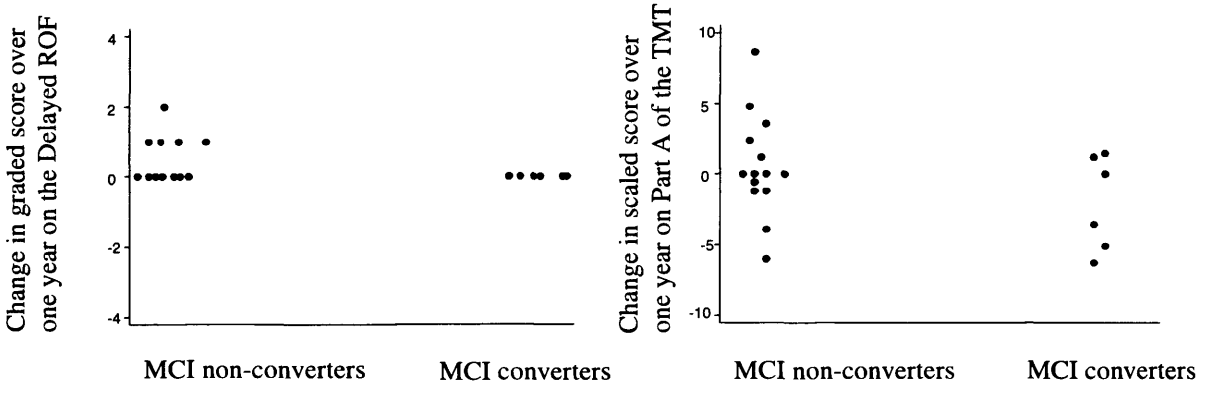


Figure 11-2 Change in performance on (a) the ROF and (b) the TMT over one year in the MCI converters and non-converters

11.2.4.2.2. Change in neuropsychology compared with CDR at one year

The relationship between change in neuropsychological performance and outcome was then assessed whilst adjusting for scores at baseline and one year on the CDR sum of boxes. This adjustment was done to assess whether the information provided by the neuropsychological tests was in addition to that provided by the change in functional rating over one year. There was still evidence of a relationship between poor clinical outcome at 2 years and change in GNT over one year ($p<0.001$).

11.2.4.2.3. Baseline neuropsychological scores and outcome 1

Baseline scores were assessed for their association with clinical outcome at two years. The results are shown in table 11-9.

Table 11-9 Baseline neuropsychological scores associated with a diagnosis of AD at two years

Outcome	P-value	Difference in baseline scaled score between converters and non converters	Confidence intervals
WASI vocab	0.009	3.3	0.9, 5.6
TMT B*	0.024	-2.4	-4.5, -0.4

***After adjustment baseline scaled score on Part B of the TMT was 2.4 points lower in the MCI converters than in the non-converters (95% CI –4.5, -0.36).**

There was evidence of an association between a poor performance on Part B of the TMT at baseline and development of AD over 2 years.

There was also evidence of a relationship between baseline score on the WASI vocabulary subset and clinical diagnosis at 2 years. This relationship would not normally be expected, as measures of IQ remain relatively stable until much later in the disease process. This incongruous result most likely reflects that on the whole the MCI converters were high performing individuals. To investigate this further we used the WASI vocabulary subset as a measure of IQ and optimal premorbid functioning and related this baseline scaled score to the baseline scaled scores from WASI matrices and the TMT Part B. A difference score was calculated by subtracting the matrices and

TMT Part B score at baseline respectively from that of the WASI vocabulary (also at baseline). Comparison of these two discrepancy scores was made between the converters and non-converters using a t-test and the results are shown in table 5. These results suggest that, whilst the converters scored relatively well on the WASI vocabulary, for this level of functioning they were performing comparatively poorly to the non-converters on the WASI matrices and TMT part B.

Table 11-10 Mean difference in scaled scores between the WASI vocab and WASI matrices, and WASI vocab and TMT Part B.

T-test results are given for the comparisons between these two difference scores, standard deviations are in brackets

	MCI converters	MCI non converters	T-test
Mean (SD) Difference Wasivocab/Wasimatrices	2.8 (3.4)	-2.1 (2.7)	P=0.002
Mean (SD) Difference Wasivocab/ TMT Part B	6.68 (3.1)	1.25 (3.3)	P=0.003

11.2.4.2.4. Follow-up neuropsychological scores and outcome 1

At one year, decreased scores on both Part A and Part B of the TMT differentiated the converters from non-converters (P=0.049, P=0.35 respectively). Performance on the CVLT delayed recognition test and ROF Immediate Recall was also significantly different between these two groups (P=0.03, P=0.038 respectively). This more likely reflected an improvement in performance in the non-converters than any real change in performance in the converters who were likely to have been scoring at floor on these tests already.

11.2.4.2.5. Baseline and follow-up neuropsychological performance and performance on the CDR over one year.

When the relationship between baseline and follow-up neuropsychological performance was adjusted for change in CDR over one year, evidence remained only of a

relationship between baseline performance on the TMT part B and clinical outcome (p=0.027).

11.2.4.2.6. Change in neuropsychology and sum of boxes at two years

Evidence of a relationship existed between change in score on the TMT part B, and the ROF delayed recall test and the sum of boxes at 2 years (TMT p=0.038, ROF P=0.03). The relationship between TMT part B and the sum of boxes at 2 years was maintained when adjustment was made for a change in the sum of boxes over one year (p=0.034).

11.2.4.2.7. Neuropsychological performance at baseline and outcome 2

Tables 14 and 15 show the relationship between the 2-year sum of boxes and baseline neuropsychological performance

Table 11-11 Baseline scores and their association with the sum of boxes at two years in the MCI group

Outcome	P-value	Effect size*	95% Confidence interval
WASI vocab*	0.045	1.3	0.03, 2.6
VOSP	0.015	1.1	0.2, 2.0
GNT	0.004	1.5	0.2, 2.0

***After adjustment each unit increase in the sum of boxes at 2 years was associated with an increase of 1.3 scaled scores on the WASIvocab at baseline.**

Only the relationship between GNT (p=0.014) and outcome remained significant once adjusted for performance on CDR over one year.

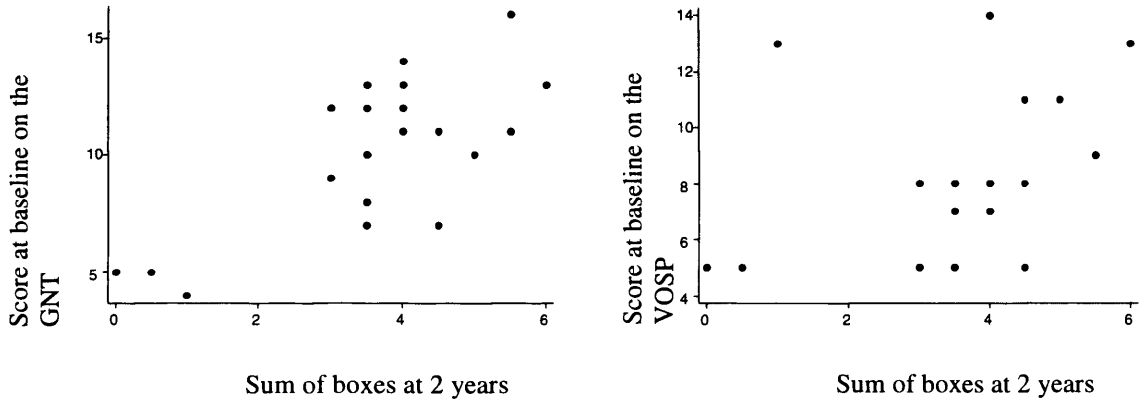


Figure 11-3 Relationship between the sum of boxes at two years and baseline performance on the (a) GNT and (b) VOSP in the MCI group

11.2.4.2.8. One-year neuropsychological performance and outcome 2

Table 11-12 One-year scores and their association with the sum of boxes at two years in the MCI group

Outcome	P-value	*Effect Size	Confidence intervals
WASI matrices*	0.025	1.1	0.2, 2.1
WASI FSIQ	0.004	5.3	1.9, 8.6
GNT	0.007	1.6	0.5, 2.7

***After adjustment each unit increase in the sum of boxes at 2 years was associated with an increase of 1.1-scaled score on the WASI matrices at one year.**

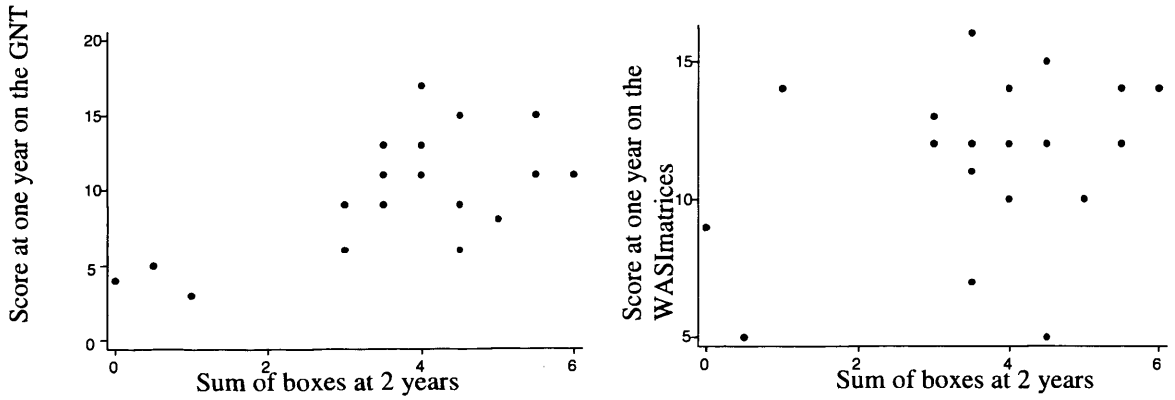


Figure 11-4 Relationship between the score at one year on the GNT and WASImatrices and the sum of boxes at two years in the MCI group

Only the relationship between WASI matrices ($p<0.001$) and WASI fsiq ($p=0.003$) and outcome remained significant once adjusted for performance on CDR over one year.

11.2.4.2.9. MCI discussion

Taken as a whole group compared to the control group, the MCI showed a decrease in performance on tests of memory, global cognition and naming over a one-year interval.

Naming and executive functioning were two domains commonly affected in the MCI converters compared to the non-converters. Lower baseline and one-year scores (TMT), and a decrease in annual performance (GNT) were associated with a clinical diagnosis of AD. Decrease in annual performance on the TMT was significantly associated with increased sum of boxes at 2 years. These relationships were independent of the change in sum of boxes over one year, suggesting that, allowing for clinical change over one year, additional information with regards to outcome can be gained from neuropsychological performance on these tests.

With established mild cognitive impairment, domains of cognition in addition to memory are recruited into the spectrum of deficits. Our findings of change in performance on the GNT are consistent with other studies (Galvin et al. 2005;Saxton et al. 2004). Galvin et al (Galvin et al. 2005) found that as many as 6 years prior to a diagnosis of AD, subtle changes on the Boston Naming Test were markers of future disease progression. Executive function is a domain which can be affected early in the course of AD, and a poor performance at baseline on this test is consistent with future conversion from MCI to AD (Blacker et al. 2007). Silveri et al (Silveri et al. 2007) recently demonstrated in their CDR-defined MCI subjects that conversion to AD was associated with lower scores on tests of attention and executive functioning. A meta analysis of studies of preclinical AD found that attention, verbal learning and memory, executive functioning, processing speed and language were the domains most commonly associated with progression to AD (Twamley et al. 2006).

This analysis disclosed two unexpected findings. First, the MCI converter group displayed a relatively strong performance on the WASI vocabulary subset. Secondly, higher scores on measures of IQ at baseline appeared to be linked to an increase in disease severity (as measured by the sum of boxes at 2 years). High baseline WASI vocabulary scores in the MCI were thought to be related to sampling error in our small cohort, where those subjects who converted to a diagnosis of AD were most likely high-functioning individuals. Similarly to the SNCI group, this finding highlights the usefulness of 'discrepancy scores' when assessing neuropsychological performance. Comparison of performance on the WASI vocabulary subset with that of the WASI matrices and Trail making test in both groups demonstrated that the MCI converters were performing more poorly on those tests of reasoning and executive function than might have been expected for their WASI vocabulary score. This discrepancy in performance is consistent with a group of individuals with early AD and might not have been apparent if absolute scores were considered alone.

Secondly, higher scores at baseline and follow-up on measures of performance IQ and naming were associated with increased disease severity at two years, measured by the CDR sum of boxes. As previously discussed, a high score on the sum of boxes at two years is not equivalent to a diagnosis of AD, and indeed in the MCI there was no relationship found between outcome 1 and outcome 2. As such one further explanation for this seemingly incongruous finding is that in highly functioning individuals (as indicated by high IQ scores), changes in perceived disease severity (change in sum of boxes over two years) may be greater if the level of functioning is higher at disease onset. Alternatively, as already discussed, this finding could simply be the result of small study numbers and resultant sampling error as described in the preceding discussion.

Over the course of this study six subjects were given a diagnosis of AD, but it is likely that others will attain this diagnosis with further follow-up. The neuropsychological tests which are likely to predict ultimate decline may vary depending upon which point in time is chosen to assess these changes. Despite this variability we have shown that neuropsychological assessments, and change in neuropsychological performance over time do provide useful information with respect to future clinical diagnosis and disease severity.

12 Conclusions and summary

As knowledge of the pathogenesis of AD has increased, it has become apparent that changes in cerebral structure and function can take place prior to the development of symptoms of the disease. Accordingly it has been important to develop clinical tools to detect these early changes and improve characterisation of the disease process itself. The ultimate goal is to identify individuals at risk of AD at the earliest possible stage. The use of disease-modifying treatments early in the disease process when there is a lower burden of amyloid and hyperphosphorylated tau is likely to have a greater effect on preservation of cognitive function than at a point when clear functional disability and cognitive impairment are present. The identification of individuals with mild disease will also be important in providing an appropriate population within which to assess the benefits of these therapies.

This thesis describes a cohort of individuals followed for a period of two years, who had sought clinical advice regarding symptoms of memory loss. All subjects were free from psychiatric or other illness that might have given rise to symptoms. All subjects had a detailed and robust neuropsychological assessment at study entry to document accurately any cognitive impairment. Our first aim was to determine whether symptoms of memory loss, change in brain appearance or alteration in cognitive performance over time could be used to predict future cognitive decline and identify individuals in the earliest stages of AD. Secondly we wished to gather information that would be useful in determining the clinical outcome and value of serial assessments in this group of patients.

We have shown that symptoms of memory loss are clinically important, even in the absence of demonstrable cognitive impairment. In this study patients with isolated symptoms of memory loss had increased conversion rates to MCI or AD compared with that found within the general population, despite the younger age range of our cohort (6% per year compared to 1-2% per year in the elderly population). Where memory symptoms were combined with evidence of memory impairment, conversion rates were even higher, at 15% per year.

Intergroup comparisons (SNCI, MCI, Controls) showed that both cross-sectional and longitudinal measurements of brain, ventricular and hippocampal volumes were

significantly different between the MCI and the SNCI and control groups. Baseline and longitudinal neuropsychological assessments were also sensitive to intergroup differences. The MCI as a group demonstrated lower scores on a wide range of cognitive domains in comparison to the other groups.

Some subjects in the SNCI group revealed changes in brain appearance with neuroimaging in as short a period as one year, and these changes were associated with future cognitive decline. Increased rates of whole brain and hippocampal atrophy and ventricular enlargement were demonstrable in those subjects who converted to MCI or AD at 2 years. This relationship was independent of clinical information regarding disease severity over a similar period. Although useful information was also gained from cross-sectional ventricular and hippocampal measurements, longitudinal measures of cerebral atrophy were better associated with outcome at 2 years.

Due to small numbers for comparison and a large variety of variables affecting neuropsychological performance and its assessment, conclusions were more difficult to draw from our neuropsychological analysis within the SNCI. Despite this difficulty at a group level measures of change in memory performance over one year were consistently associated with future cognitive decline. However, most value in this analysis was derived from assessing neuropsychological performance on a case-by-case basis, noting whether discrepancies were present between scores on either visual or verbal memory tests, or whether progressive decline was apparent on serial assessments.

Finally this study has shown that even where strict inclusion and exclusion criteria are employed, the SNCI subjects tend to form a heterogeneous group, with variation in neuropsychological performance, neuroimaging changes, clinical status and likely underlying disease process. Nevertheless, it is still possible to use sequential data to identify those individuals with early cognitive decline who will progress to MCI or AD. Clearly these individuals are the most likely to benefit from treatment.

Although increased rates of cerebral change were significantly different between the MCI and the Controls and SNCI groups, this measure was not so useful when the MCI group was divided into MCI-converters and non-converters. Neuropsychological performance over one year did differ between these two sub groups, with changes in executive function and naming showing the greatest association with outcome at 2 years. However, there may be a certain circularity to this relationship, as elements from these neuropsychological assessments were used to assign a diagnosis of AD at 2 years.

No correlation was found between our clinical disease severity rating (Clinical Dementia Rating) and clinical diagnosis at 2 years. This is an important observation because many groups have used these two measures interchangeably both to define patient groups at study outset and as outcome measures at the end of a period of follow-up. Our work suggests that these two measures are not necessarily related and may provide different information about the same disease process. Furthermore, our work highlights the difficulties in choosing a predetermined time point for the end of a study. Clinical assessment at one particular point in time may not reflect the underlying disease burden of a group, and consequently longitudinal follow-up (to post mortem if possible) is essential to be sure of the actual numbers with AD.

The findings from this study are clinically applicable. First, symptoms of memory loss are important irrespective of the presence of demonstrable cognitive impairment. Second, serial neuropsychological and neuroimaging assessments are of great value when assessing individuals with symptoms of memory loss, and provide information regarding possible future cognitive decline. Third, rates of cerebral change showed a stronger association with future cognitive decline than cross-sectional volumes. Fourth, should serial neuroimaging be incorporated into regular clinical investigations with measures of cerebral change used in a clinical rather than scientific context, it is imperative that careful protocols regarding head positioning and consistent metal removal are carried out. As we have shown, failure to do so can seriously compromise the quality of subsequent scan registration. This is also an important consideration where rates of cerebral atrophy measured by serial MRI scans are used as surrogate markers for disease progression in clinical trials. These studies often involve many investigative centres, which can increase the likelihood of scanner and procedure variability.

Our study reports findings from a well-classified and characterised cohort of individuals at an earlier stage of AD than that described by the majority of 'early AD' studies. Most studies to date have assessed either asymptomatic individuals who have become demented, or else included a wide range of memory impairment in their 'preAD' cohorts. Our study represents a group of subjects (SNCI) that commonly present for assessment at memory clinics. We have shown that this group is at increased risk of future cognitive decline. This increased risk of decline is detectable using serial

neuroimaging and neuropsychological assessments. These findings supplement and extend the currently available literature. Although the results of our own investigation are relevant to a clinical population, it is important to note that maximising specificity for a diagnosis of AD within this small cohort (using strict exclusion and inclusion criteria) may have resulted in a substantial loss of sensitivity, as some of the subjects excluded from this cohort, as well as individuals not referred to our memory clinic, may have underlying diagnoses of AD.

Recently a proposal has been put forward to move away from the traditional NINCDS-ADRDA criteria for a diagnosis of AD and towards a clinical core of early AD signs (memory impairment) supported by neuroimaging findings (Dubois et al. 2007) to identify patients with underlying AD at an earlier stage. In this context a 'preMCI' stage, identifiable with neuroimaging or neuropsychological markers as in our study, becomes increasingly relevant. Future follow-up of our cohort will prove invaluable (with post mortem evaluation) to confirm the end diagnosis in these individuals and also ascertain whether other subjects within the SNCI and aMCI groups also converted to a diagnosis of MCI or AD.

We believe this body of work has contributed to current knowledge regarding the natural course of AD and will continue to provide information by mapping the clinical, neuroimaging and neuropsychological changes taking place over time in individuals with sporadic AD. Future follow-up assessments will allow a definitive answer as to whether the SNCI group is heterogeneous, or whether all subjects convert to a diagnosis of MCI or AD several years later, and also whether the MCI were truly a homogeneous group. Further replication of this protocol in a larger study group will also strengthen the findings of this study.

Study Limitations

Although this study has allowed useful observations to be made regarding the early stages of cognitive decline, there are several limitations to this work and the application of its findings. First, as in many neuroimaging studies, the number of subjects has been necessarily limited and the overall cohort size is small. This restricted the degree of analysis that could be carried out, for example, limiting our ability to identify neuropsychological risk factors for disease progression and the extent of the conclusions

that could be drawn from the demographic and neuroimaging data. Our conversion rates (for both SNCI to MCI or AD and MCI to AD) were higher than those of other studies, and allowed us to draw several meaningful conclusions; however the total number of converters and non converters where not large enough to fully investigate the typology of those who would exhibit progressive cognitive decline from those who wouldn't. Second, it is of note, that this is a clinical not a community based study. All subjects sought help from health professionals for memory difficulties prior to referral for this study. Furthermore, our subjects were on average, of a younger age than the majority of patients who routinely present to general practice and psychiatry clinics with memory symptoms. As such our cohort is unlikely to be entirely representative of the general population. This means that application of these results to the general population must be done with care. Although the methods used in this study were effective at screening for PreMCI in our cohort, this may not result if they were applied to the population at large. Ideally this study would be replicated using a community based cohort to ensure that the findings hold true for the general population. Fourth, although MRI is a powerful tool for imaging cerebral disease, there are many limitations to its use; these include its availability and cost, as well as operator expertise and reproducibility (as we found in this study). MRI may not be susceptible to the influences of depression or anxiety in the same way as cognitive tests, however it is not readily transportable to patients, and is not appropriate in those with metal implants or who are claustrophobic. The use of cognitive tests has been well validated in many studies, and they are relatively inexpensive and easy to carry out, however as we have mentioned in this study they also have their own limitations, including practice effects, and floor and ceiling effects. Finally, specific to this work, although the clinicians determining the 2 year diagnoses had no prior involvement in the study, they were not blind to its overall purpose. It is possible that this may have introduced a degree of bias to our results.

Novel findings, clinical applications and future research

This study has provided several novel findings, with applications to both clinical practice and research studies. First, we have carefully characterised a group of individuals who routinely present to memory clinics with symptoms of memory loss, but no cognitive impairment. We have shown that this group is likely to be heterogeneous in nature (in terms of memory symptom aetiology) with only a small, yet

significant proportion converting to MCI or AD each year. Description of this cohort has added to the currently available information on a 'PreMCI' stage, and is consistent with what is already known on this subject. Furthermore, we have found that certain aspects of the clinical history, namely use of memory aids and informant ratings, as well as qualitative assessments of hippocampal size, can give an indication of how impaired an individual is likely to be on tests of memory. The clinical application of these findings is that high informant concern, low use of memory aids and qualitatively small hippocampi could potentially be useful in an outpatient setting in identifying individuals who are likely to have cognitive impairment and should have neuropsychological assessment and continued follow up. As outlined previously, there are limitations to how widely these findings can be applied, but they should at least be applicable to patients attending early-onset memory clinics. Our two-year follow up revealed that there was a significantly higher rate of conversion to MCI or AD in those with symptoms of memory loss but no cognitive impairment (6% per year), than in either our healthy control group, or the general population (1-2% per year), and therefore that symptoms of memory loss are associated with a greater likelihood of future cognitive decline, albeit within the confines of our selected study population. Again, the clinical application of this finding is that symptoms of memory loss, should be taken seriously when a subject seeks help for memory problems. Finally, the longitudinal data revealed that change in rates of cerebral atrophy can be used to identify which subjects with symptoms of memory loss but no cognitive impairment will experience further cognitive decline over the next two years. This is consistent with studies which have demonstrated increased rates of cerebral atrophy in presymptomatic individuals with familial AD. This again, is a novel finding, and may have a potential future application in identifying individuals for whom preventative treatments for AD would yield a very real benefit.

Despite these findings, there is still a very large gap between this work - identifying individuals at risk of AD, after they have sought medical help and have been screened for a wide variety of other underlying causes for memory loss (depression, anxiety, vascular disease), and using these tools to screen for early AD in the general population. Serial neuroimaging and neuropsychological assessments, such as used in this study are unlikely to be routinely available to health professionals such as general practitioners. Furthermore, it needs to be considered whether in the absence of an effective disease modifying treatment, and with restrictions placed upon prescription of symptomatic

treatments, whether it is useful at present to identify individuals with presymptomatic AD when there is very little to offer apart from supportive therapies.

Future directions for this study will include ascertainment of whether these findings are indeed reproducible in the general population and to assess which investigative tools identified from this study so far could be used for future screening for early AD. Future work will also involve further follow up of this cohort, to assess whether the SNCI remain a heterogeneous group, and to determine what proportion of these subjects convert to MCI or AD in the long term. Are a large proportion of these subjects truly at risk of AD or will the majority continue to have memory symptoms but no discernible impairment? Future follow up will also reveal which MCI subjects will go on to develop AD, how our conversion rates compare with other studies over similar periods of follow up, and with larger conversion numbers, may also permit examination of which factors point to an increased likelihood of conversion to AD in the MCI. Finally, a further aim is to clarify which factors (symptom length, APOE4 etc.) are associated with a future diagnosis of AD, and to use these to identify individuals appropriate for initially, early intervention clinical treatment trials and in the long term, potentially disease modifying therapies prescribed in clinical practice.

Summary

Symptoms of memory loss in the absence of cognitive impairment are clinically important, and serial neuroimaging and neuropsychological assessments are helpful in identifying those individuals with symptoms who are likely to progress to a diagnosis of AD. Further follow-up of this cohort is of great interest in order to ascertain the long-term outcome of this well-characterised group of individuals.

Publications

Publications arising from this thesis

Archer HA, McFarlane F, Frost C, Cutler D, Fox NC, Rossor MN. Symptoms of memory loss as predictors of cognitive impairment?: the use and reliability of memory ratings in a clinic population. *Alzheimer Dis Assoc Disord.* 2007 Apr-Jun; 21(2):101-6.

Archer HA, MacFarlane F, Price S, Moore EK, Pepple T, Cutler D, Frost C, Fox NC, Rossor MN. Do symptoms of memory impairment correspond to cognitive impairment: a cross-sectional study of a clinical cohort.
Int J Geriatr Psychiatry. 2006 Dec; 21(12): 1206-12.

Archer HA, Schott JM, Barnes J, Fox NC, Holton JL, Revesz T, Cipolotti L, Rossor MN. Knight's move thinking? Mild cognitive impairment in a chess player. *Neurocase.* 2005 Feb;11 (1): 26-31.

Book chapters arising from this thesis

Barnes J, **Archer H**, Fox NC. 2007. Imaging Cerebral Atrophy in Alzheimer's Disease. In Research Progress in Alzheimer's disease and Dementia (pp.403-435). New York: Nova Science Publishers.

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I would also like to thank Anthony,Benjamin and Oscar Edey and Desmond and Amelia Archer for all their support during my thesis, and for their continued interest in my work.

Appendix

1 Criteria for the diagnosis of dementia

Diagnostic and Statistical Manual of Mental Disorders (4th Edition) (DSM-IV)(DSM-IV 1994)

I. The development of multiple cognitive deficits manifested by both:

a) Memory impairment
Impaired ability to learn new information or recall learned information

b) and one (or more) of the following cognitive disturbances:

(i) Aphasia
language disturbance

(ii) Apraxia
impaired ability to carry out motor activities despite intact motor function

(iii) Agnosia
failure to recognise or identify objects despite intact sensory function

(iv) Disturbance in executive functioning
i.e., planning, organizing, sequencing, abstracting

II. The cognitive deficits in Criteria Ia and Ib each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning

III. The deficits do not occur exclusively during the course of a delirium

Dementia is diagnosed if criteria I, II and III are met
(Note that only one of the features listed under Ib has to be present)

2 Criteria for the diagnosis of Alzheimer's disease

National Institute of Neurological and Communicative Disorders and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al. 1984)

Probable Alzheimer's disease (if all criteria I are answered with 'yes')

I. The diagnosis of PROBABLE Alzheimer's disease requires:

a) Dementia established by clinical examination and documented by the MMSE; Blessed Dementia Scale, or similar examination, and confirmed by 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 ages 40 and 90, most often after age 65
f) Absence of systemic disorders or other brain disease that in and of themselves could account for the progressive deficits in memory and cognition

II. The diagnosis of PROBABLE Alzheimer's disease is supported by:

a) Progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perceptions (agnosia)
b) Impaired activities of daily living and altered patterns of behaviour
c) Family history of similar disorders, particularly if confirmed neuropathologically
d) Normal lumbar puncture as evaluated by standard techniques
e) Normal pattern of EEG change, e.g. increased slow wave activity
f) Evidence of cerebral atrophy on CT with progression documented by serial observation

III. Other clinical features consistent with PROBABLE Alzheimer's disease:
a) Plateaus in the course of progression of the illness

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

Score	Memory	Orientation	Judgement and problem solving	Community affairs	Home and hobbies	Personal care
Healthy: CDR 0	No memory loss or slight inconsistent forgetfulness	Fully orientated	Solves everyday problems and business and financial affairs well; judgement good in relation to past performance	Independent function at usual level in job, shopping, volunteer and social groups	Life at home, hobbies, intellectual interests well maintained	Fully capable of self care
Questionable: CDR 0.5	Consistent slight forgetfulness; partial recollection of events; 'benign' forgetfulness	Fully orientated except for slight difficulty with time relationships	Slight impairment in solving problems, similarities, differences	Slight impairment in these activities	Life at home, hobbies, intellectual interests slightly impaired	Needs prompting
Mild dementia: CDR 1	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Moderate difficulty with time relationships; orientated for place at examination; may have geographic disorientation elsewhere	Moderate difficulty in handling problems, similarities, differences; social judgement usually maintained	Unable to function independently at these activities though may still be engaged in some; appears normal to casual inspection	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Requires assistance in dressing, hygiene, keeping of personal effects
Moderate dementia: CDR 2	Severe memory loss; only highly learned new material retained; new material rapidly lost	Severe difficulty with time relationships; usually disorientated in time, often to place	Severely impaired in handling problems, similarities, differences; social judgement usually impaired	No pretense of independent function outside home. Appears well enough to be taken to functions outside the family home	Only simple chores preserved; very restricted interests, poorly maintained	Requires much help with personal care; frequent incontinence
Severe dementia: CDR 3	Severe memory loss, only fragments remain	Orientated to person only	Unable to make judgements or solve problems	No pretense of independent function outside home. Appears too ill to be taken to functions outside family home	No significant function in home	

4 Clinical anxiety scale – abridged version

(Snaith et al. 1982)

Psychic tension

Score 4	Very marked and distressing feeling of being 'on edge', 'keyed up', 'wound up' or 'nervous' which persists with little change throughout the waking hours
Score 3	As above, but with some fluctuation of severity during the course of the day
Score 2	A definite experience of being tense, which is sufficient to cause, some, although, not severe distress
Score 1	A slight feeling of being tense which does not cause distress
Score 0	No feeling of being tense apart from the normal degree of tension experienced in response to stress and which is acceptable as normal for the population

Ability to relax

Score 4	The experience of severe tension throughout much of the bodily musculature which may be accompanied by such symptoms as pain, stiffness, spasmodic contractions, and lack of control over other movements. The experience is present throughout most of the waking day and there is no ability to produce relaxation at will
Score 3	As above, but the muscular tension may only be experienced in certain groups and may fluctuate in severity throughout the day.
Score 2	A definite experience of muscular tension in some part of the musculature sufficient to cause some, but not severe, distress.
Score 1	Slight recurrent muscular tension of which the patient is aware but which does not cause distress. Very mild degrees of tension headache or pain in other groups of muscles should be scored here.
Score 0	No subjective muscular tension or of such a degree which, when it occurs can easily be controlled at will.

Startle response (hyperarousability)

Score 4	Unexpected noise causes severe distress so that the patient may complain in some such phrase as 'I jump out of my skin'. Distress is experienced in psychic and somatic modalities so that there is a muscular activity and autonomic symptoms such as sweating or palpitations.
Score 3	Unexpected noise causes severe distress in psychic or somatic, but not other modalities
Score 2	Unexpected noise causes definite but not severe distress.
Score 1	The patient agrees that he is slightly 'jumpy' but is not distressed by this.
Score 0	The degree of startle response is entirely acceptable as normal for the population.

Worrying (The assessment must take into account the degree to which worry is out of proportion to actual stress)

Score 4	The patient experiences almost continuous preoccupation with painful thoughts which cannot be stopped voluntarily and the distress is quite out of proportion to the subject matter of the thoughts.
Score 3	As above, but there is some fluctuation in intensity throughout the waking hours and the distressing thoughts may cease for an hour or two, especially if the patient is distracted by activity requiring his attention.
Score 2	Painful thoughts out of proportion to the patient's situation keep intruding into consciousness but he is able to dispel or dismiss them.
Score 1	The patient agrees that he tends to worry a little more than necessary about minor matters but this does not cause much distress.
Score 0	The tendency for worry is accepted as being normal for the population; for instance even marked worrying over a severe financial crisis or unexpected illness in a relative should be scored as 0 if it is judged to be entirely in keeping with the degree of stress.

Apprehension

Score 4	The experience is that of being on the brink of some disaster which cannot be explained. The experience need not be continuous and may occur in short bursts several times a day.
Score 3	As above, but the experience does not occur more than once a day.
Score 2	A sensation of groundless apprehension of disaster which is not severe although it causes definite distress. The patient may not use strong terms such as 'disaster' or 'catastrophe' but may express his experience in some such phrase as 'I feel as if something bad is about to happen'
Score 1	A slight degree of apprehensiveness of which the patient is aware but which does not cause distress
Score 0	No experience of groundless anticipation of disaster

5 Geriatric depression scale

(Sheikh VI and Yesavage VA 1986)

1 Are you basically satisfied with your life Yes/**No**

2 Have you dropped many of your activities and interests? **Yes**/No

3 Do you feel happy most of the time? Yes/**No**

4 Do you prefer to stay at home rather than going out and doing new things? **Yes**/No

If none of the above responses suggests depression, STOP HERE. If any of the above responses suggests depression ask questions 5-15.

5 Do you feel that life is empty? **Yes**/No

6 Do you often get bored? **Yes**/No

7 Are you in good spirits most of the time? Yes/**No**

8 Are you afraid that something bad is going to happen to you? **Yes**/No

9 Do you feel helpless? **Yes**/No

10 Do you feel that you have more problems with memory than most? **Yes**/No

11 Do you think that it is wonderful to be alive? Yes/**No**

12 Do you feel pretty worthless the way you are now? **Yes**/No

13 Do you feel full of energy? Yes/**No**

14 Do you feel that your situation is hopeless? **Yes**/No

15 Do you think that people are better off than you are? **Yes**/No

6 Study protocol sheet

Name	
QSC number	
Address	
Telephone	
Address for correspondence	
GP name and address	
Travel arrangements	
DOB	
Age at baseline	
Sex	

Support/carer	
Informant	
Informant (i)relationship to patient (ii) Length of acquaintance (iii) How often do they see them	
Age at onset of symptoms: Subject Informant	
Present occupation and occupational history	
Best academic qualification	
School leaving age	
First language	
Race/ethnicity	
Handedness	

PMH Include details and date of event/diagnosis:

Hypertension	
CVA/TIA	
PVD/known increased cholesterol	
MI/IHD	
Diabetes mellitus	
Head injury	
Seizures/meningitis	
Psychiatric history ECT	

Other PMH:	

Smoker duration	
Alcohol units/week current and history	
Lives alone/care/ nursing/residential home	
Family history Document negative family history	

Current drugs - date started	

Questions

Memory Do you feel that you have problems with your memory relative to people of your own age?

Subject YES / NO (circle as appropriate)

Informant YES / NO (circle as appropriate)

Physical examination features:

General examination

	Date			Date			Date		
	Yes	No	description	Yes	No	description	Yes	No	description
Blood pressure									
Pulse rate									
Cardiovascular abnormality									
Abdominal abnormality									
Gastrointestinal abnormality									
Respiratory abnormality									

Neurological Examination

	Date			Date			Date		
	Yes	No	description	Yes	No	description	Yes	No	description
Visual field abnormality									
Eye movement abnormality									
Facial asymmetry									
Myoclonus									
Extrapyramidal signs									
Dysathria/ bulbar features									
Abnormal limb tone									
Finger extension /abduction									
Reflexes abnormal									
Plantar response									
Apraxia									
Other significant									

Investigations

Bloods pre-baseline

test	FBC	Biochem	HbA1C	TFT	B12	ESR	Cholesterol	Homocysteine
date								
result								
abnormal								

Questionnaires

Date			
MF			
CAS			
GDR			
CDR – total			

Previous MRI or EEG?

Date	Result
Date	Result

Changes from last visit:

Month	0	12	24
Date			
Medicines			
Illness			
Cognition			
Seizure			
Head injury			
Contra-indication to scan			

Drop out date	
Reason	

7 Memory functioning questionnaire

(Gilewski and Zelinski 1988)

General frequency of forgetting

How would you rate your memory problems in terms of the kinds of problems that you have?

Major problems			Some minor problems			No problems
1	2	3	4	5	6	7

How often do these present a problem for you?

	Always			Sometimes			Never
	1	2	3	4	5	6	7
Names	1	2	3	4	5	6	7
Faces	1	2	3	4	5	6	7
Appointments	1	2	3	4	5	6	7
Where you put things (e.g. keys)	1	2	3	4	5	6	7
Performing household chores	1	2	3	4	5	6	7
Directions to places	1	2	3	4	5	6	7
Phone numbers you've just checked	1	2	3	4	5	6	7
Phone numbers you use frequently	1	2	3	4	5	6	7
Things people tell you	1	2	3	4	5	6	7
Keeping up with correspondence	1	2	3	4	5	6	7
Personal dates (e.g. birthdays)	1	2	3	4	5	6	7
Words	1	2	3	4	5	6	7
Going to the shop and forgetting what you wanted to buy	1	2	3	4	5	6	7
Taking a test	1	2	3	4	5	6	7
Beginning to do something and forgetting what you were doing	1	2	3	4	5	6	7
Losing the thread of thought in conversation	1	2	3	4	5	6	7
Losing the thread of thought in public speaking	1	2	3	4	5	6	7
Knowing whether you've already been told something by someone	1	2	3	4	5	6	7

Memory Stratagems

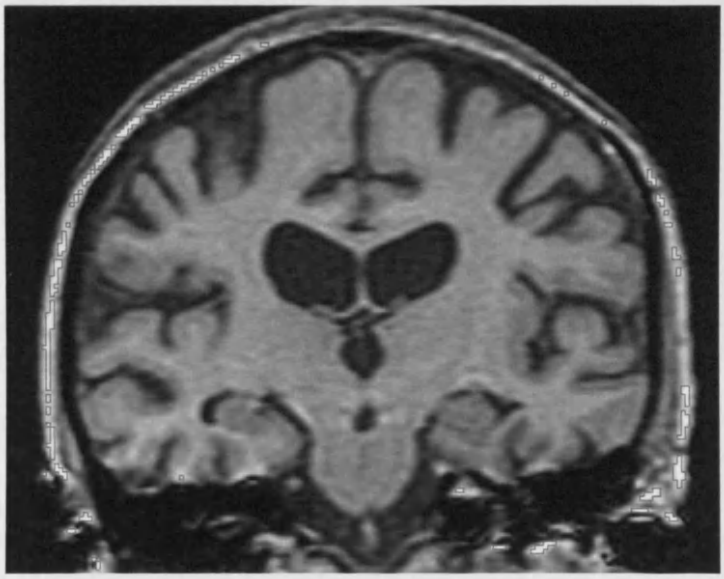
How often do you use these techniques to remind yourself about things?...

	1	2	3	4	5	6	7
Keep an appointment							
Write a reminders list							
Make a list of things to do							
Make grocery lists							
Plan your daily schedule in advance							
Mental repetition							
Associations with other things							
Keep things you need to do in a prominent place where you will notice them							

8 Whole brain segmentation protocol

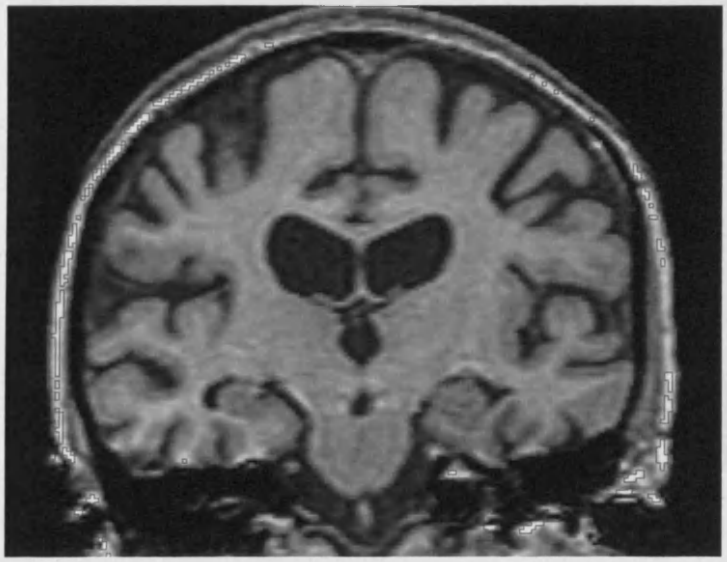
Whole brain segmentation was performed using a protocol described in detail by Freeborough et al (Freeborough et al. 1997).

1. An upper threshold value is set to ensure that no brain tissues are outlined (Figure A1).



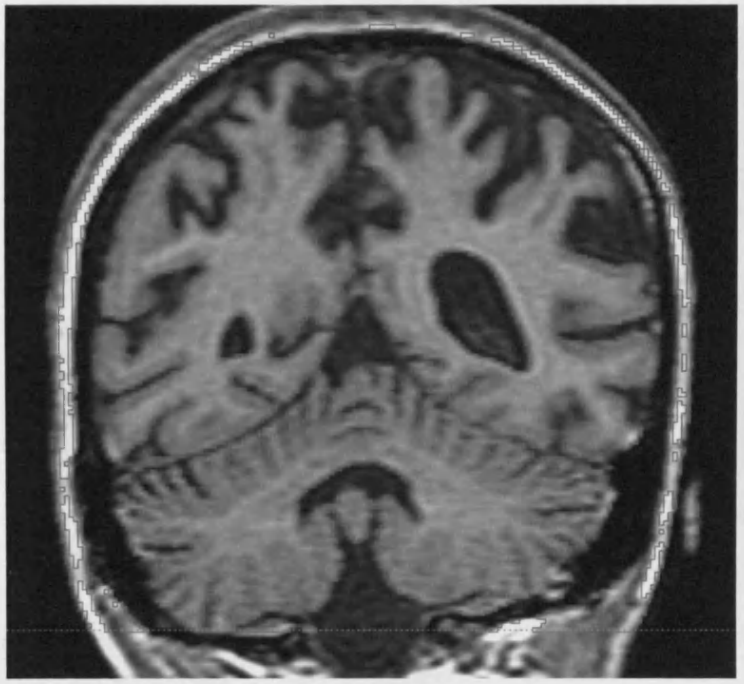
A 1 Setting the upper threshold

2. The Lower threshold is then set to a value to include the brain but not CSF. The aim is to outline the brain as accurately as possible (Figure A2).



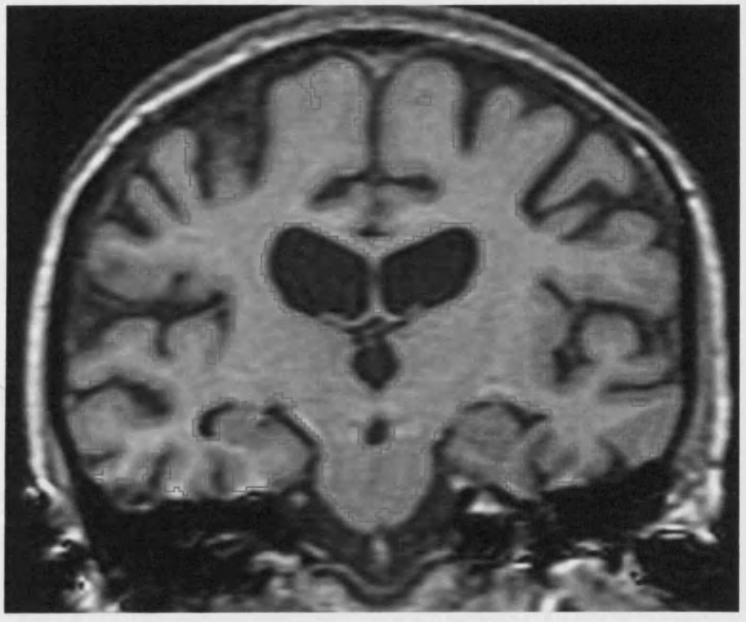
A 2 Setting the lower threshold

3 The axial cut-off is set to remove any non-brain below the cerebellum; this provides a reproducible lower/inferior limit (Figure A3).



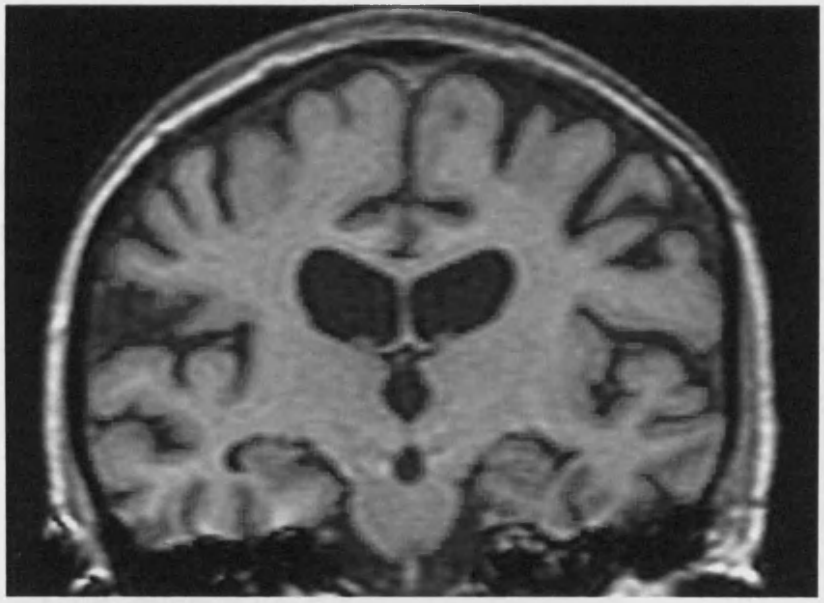
A 3 Defining the inferior limit of the scan

4 A series of erosions are applied to 'eat away' at the external surfaces of the brain region that has been outlined above until only brain remains (see Figure A4).



A 4 Using erosions to define tissue

5 A series of conditional dilations are applied to recover the brain that has been removed by the erosion process (see Figure A5) while excluding non-brain voxels.

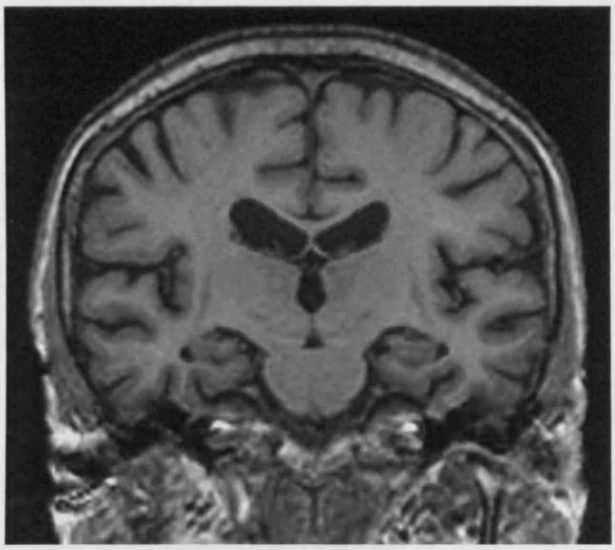


A 5 Using dilations to recover lost brain tissue

6 The final step is to apply a rethresholding box to 'fill in' any area within that region that has been omitted by step 5. Subsequent manual editing may be required to ensure that the brain is correctly outlined.

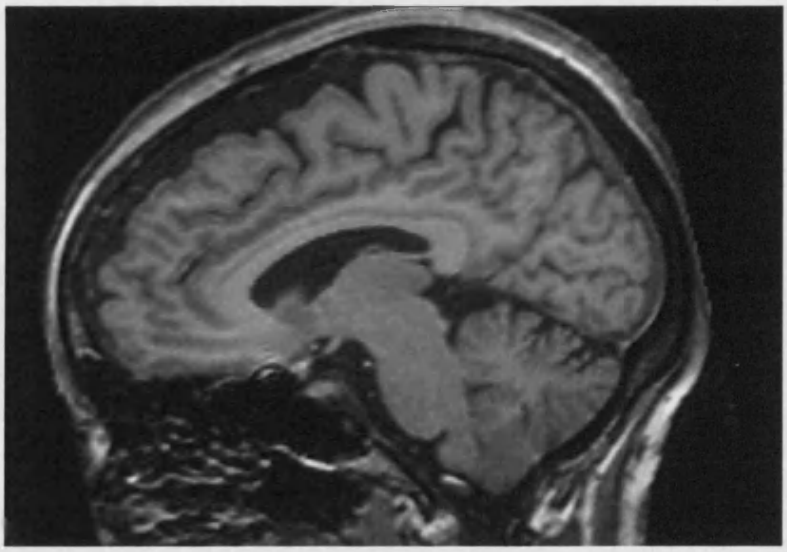
9 Ventricular segmentation protocol

The aim of the protocol is to label areas of ventricular cerebrospinal fluid, but not extraneous CSF spaces. Using the segmented whole brain (Appendix 8), a threshold of 60% mean voxel intensity value from the whole brain is used to define the ventricular spaces. ''Seeds'' are planted within the ventricles, and the outlined regions are propagated caudally and rostrally to include the lateral ventricles. Manual editing is required to ensure that extraneous CSF spaces are not included, that the temporal horns are included, and that the third but not fourth ventricle is outlined (see Figure A6)



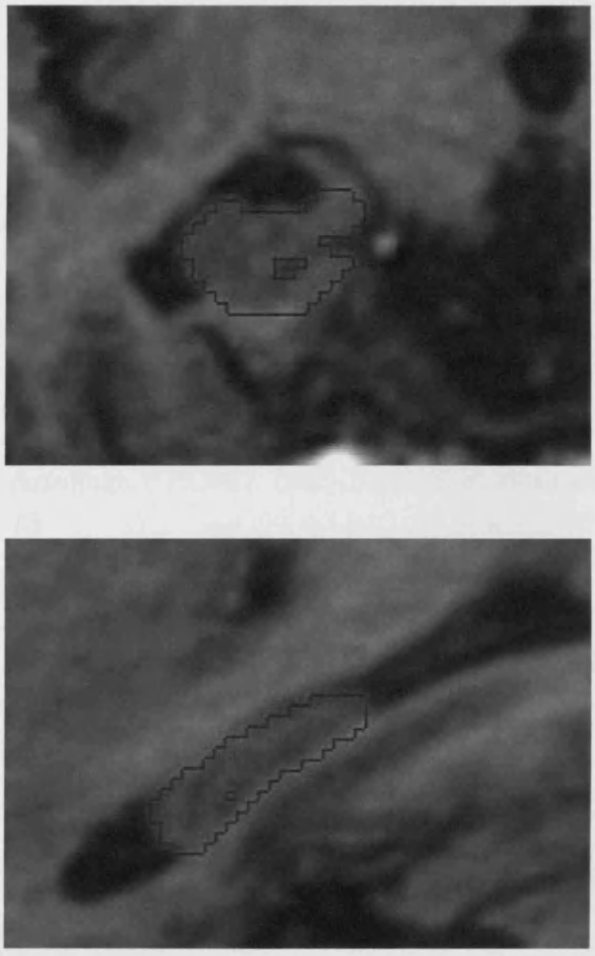
A 6 Ventricular segmentation

Coronal (upper) and sagittal (lower) views.



10 Hippocampal segmentation

The hippocampus was delineated by reference to the neuroanatomical atlas by Duvernoy (Duvernoy 1998). The caudal most measurement of the hippocampus was taken at the level of the crus (longest length) of the fornix. The rostral boundary of the hippocampus was at its junction with the amygdala. Superiorly, medially and laterally the hippocampus was bounded by the ambient cistern and temporal horn of the lateral ventricle, and inferiorly by the subjacent white matter of the subiculum. This measure included the dentate gyrus, the hippocampus proper and the alveus. The hippocampal tail was excluded in order to achieve satisfactory reproducibility of segmentation, as recommended by Watson *et al* (Watson et al. 1992).



A 7 Hippocampal segmentation

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